CLINICAL STUDY PROTOCOL

NCT Number: NCT02350816

Study Title: An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease

Study Number: SHP610-201

Protocol Version and Date:

Original Protocol: 23 September 2014
Amendment 1: 17 December 2015
Amendment 2: 25 January 2017

Clinical Trial Protocol: SHP-610-201

Study Title:	An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease
Study Number:	SHP-610-201
Study Phase:	IIb
Product Name:	HGT-1410
Device Name:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
IND Number:	102165
EUDRACT Number	2014-003960-20
Indication:	Long term treatment of Mucopolysaccharidosis Type IIIA (MPS IIIA or Sanfilippo Syndrome Type A)
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc.
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA +1-617-349-0200
Medical Monitor:	[redacted], MD

	Date
Original Protocol:	23 September 2014

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc. (Shire)

Name of Finished Product:

HGT-1410 (Recombinant Human Heparan N Sulfatase or rhHNS)

Name of Device:

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

Study Title:

An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease

Study Number:

SHP-610-201

Study Phase: IIb

Investigational Product, Dose, and Mode of Administration:
HGT-1410 at a dose of 45 mg administered every 2 weeks (Q2W) or 45 mg administered every 4 weeks (Q4W). HGT-1410 will be administered intrathecally (IT) by an indwelling intrathecal drug delivery device (IDDD).

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-1410 indicated for intrathecal delivery intermittently over a long period of time.

Comparator, Dose, and Mode of Administration:

Not applicable

Primary Objective(s):

To evaluate long-term safety in patients with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo Type A) who received HGT-1410

Secondary Objective(s):

To evaluate:

- The long-term cognitive function as measured by the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) or Kaufman Assessment Battery for Children, 2nd Edition (KABC-II), age-equivalent and developmental quotient (DQ) scores in patients with MPS IIIA who received HGT-1410
- The long-term adaptive behavioral function, assessed by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) in patients who received HGT-1410
- The total cortical grey matter volume, as assessed by volumetric MRI of the brain, in patients who received HGT-1410

Exploratory Objective

[redacted]

Pharmacokinetic and Pharmacodynamic Objectives

To evaluate:

- The pharmacokinetics (PK) of HGT-1410 in serum
- The PK of HGT-1410 in cerebrospinal fluid (CSF), in patients who received no-treatment in Study HGT-SAN-093
- The concentration of glycosaminoglycans (GAG) in CSF and urine in patients who received HGT-1410

Health Status Objective

To evaluate health status as measured by the Infant Toddler Quality of Life Questionnaire™ (ITQoL) instrument in patients who received HGT-1410

Health Economics and Outcomes Research Objectives

To evaluate healthcare resource utilization, as evaluated by the Healthcare Utilization Questionnaire (HCUQ), in patients who received HGT-1410.

Study Endpoints:

Safety evaluations include the assessment of adverse events (AEs), IDDD related issues, laboratory values, anti-rhHNS antibody development, vital signs, physical examination findings, and ECG results

The secondary endpoints of this study are:

The change from Baseline in BSID-III or KABC-II age-equivalent, DQ, and developmental delay scores
The change from Baseline in adaptive behavioral function domains, assessed by VABS II, using raw scores, age-equivalent scores, and DQ scores
The change from Baseline in total cortical grey matter volume, as assessed by MRI

[redacted]

The PK endpoint is to determine the pharmacokinetic behavior of HGT-1410 in serum. The pharmacokinetic behavior of HGT-1410 in CSF will also be determined in patients who received no-treatment in Study HGT-SAN-093.

The pharmacodynamic (PD) endpoint is to determine the GAG concentrations in CSF and urine.

The health status endpoint is the ITQoL scores at each assessment time and the corresponding change from Baseline.

The health economic and outcome research endpoints evaluate key HCUQ variables, such as the number of emergency room visits, caregiver employment status (full-time [FT], part-time [PT], or not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study.

Study Population:
A maximum of 18 patients with MPS IIIA and who completed Study HGT-SAN-093 are planned to enroll in this study.

Study Design:
This is an open-label study for patients who completed through at least the Week 48 Visit of Study HGT-SAN-093. Patients who originally received HGT-1410 in Study HGT-SAN-093 will remain on the same dosing regimen as they received in Study HGT-SAN-093; Group 1 will receive HGT-1410 Q2W and Group 2 will received HGT-1410 Q4W. Patients in Groups 1 and 2 will begin treatment at Week 50 and Week 52, respectively, of this extension study (Study SHP-610-201). Patients who originally received no-treatment in Study HGT-SAN-093 (Group 3) will receive an IDDD following informed consent and will be re-randomized in a 1:1 allocation ratio to receive HGT-1410 via a Q2W or Q4W dosing regimen (Groups 3A and 3B, respectively) in Study SHP-610-201. Patients in Groups 3A and 3B will begin treatment on Week 0 of the extension study.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all IT injections of HGT-1410. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual(s), which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug may be administered and CSF sampled by lumbar puncture (LP). General anesthesia or sedation may be required for injections of study drug and some evaluations, and can be used at the discretion of the Investigator. 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, extension study, expanded access program, commercially available etc.).

Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of Study SHP-610-201. For patients who received HGT-1410 in Study HGT-SAN-093, a serum PK sample will be obtained at the Week 96 visit (after approximately 2 full years of exposure to HGT-1410 across Study HGT-SAN-093 and SHP-610-201). For patients who received no-treatment in Study HGT-SAN-093, serum PK samples will be obtained at the Week 0, 48, and 96 visits, and CSF PK samples will be obtained on the Week 0 and 48 visits in Study SHP-610-201.

Study Duration:
Approximately 30 months of treatment with HGT-1410 will occur during the study.

Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no-treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

1. Patient has completed through at least the Week 48 visit of Study HGT-SAN-093.
2. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board- (IRB-)/Independent Ethics Committee- (IEC-) approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

Exclusion Criteria:

Patients will be excluded from the study if any of the following criteria are met:

1. The patient, if randomized to treatment in Study HGT-SAN-093, has experienced a decline of more than 20 points in the BSID-III cognitive DQ score between Baseline and the Week 48 visit in Study HGT-SAN-093, AND, upon individual evaluation by the Investigator, has been deemed a treatment failure*.
2. The patient has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with HGT-1410, including but not limited to clinically relevant intracranial hypertension, severe infusion-related reactions after treatment with HGT-1410, uncontrollable seizure disorder.
3. The patient has a known hypersensitivity to any of the components of HGT-1410.
4. The patient is enrolled in another clinical study, other than HGT-SAN-093, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT ® Mini S IDDD Instructions for Use, including:
    a The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT ® Mini S device
    b The patient's body size is too small to support the size of the SOPH-A-PORT ® Mini S Access Port, as judged by the Investigator
    c The patient's drug therapy requires substances known to be incompatible with the materials of construction
    d The patient has a known or suspected local or general infection
    e The patient is at risk of abnormal bleeding due to a medical condition or therapy
    f The patient has one or more spinal abnormalities that could complicate safe implantation or fixation

g The patient has a functioning CSF shunt device

h The patient has shown an intolerance to an implanted device

7. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations, or is otherwise unlikely to complete the study) as determined by the Investigator.

*All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in the BSID-III DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

Efficacy Assessments:

Efficacy variables to be assessed will include cognitive function expressed as a DQ assessed by neurocognitive testing using the BSID-III/KABS-II; adaptive behavioral function over time, assessed by VABS-II; the total cortical grey matter volume and liver and spleen size as assessed by magnetic resonance imagining (MRI); as well as quality of life score (assessed using the ITQoL); and health care resource utilization (assessed using the HCUQ).

Pharmacokinetic Assessments:

The determination of HGT-1410 concentration in serum for all patients and in CSF for patients who received no-treatment in Study HGT-SAN-093.

Pharmacodynamic Assessments:

The determination of GAG concentrations in CSF and urine.

Safety Assessments:

Safety will be assessed during the study by the following:

- collection of adverse events (by type, severity, and relationship to treatment [HGT-1410, the IDDD, device surgical procedure, or IT administration process])
- changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- physical examination
- vital signs
- 12-lead electrocardiogram (ECG) recordings
- CSF laboratory parameters (chemistries, cell counts)
- anti-rhHNS antibodies in CSF and serum, including determination of antibodies having enzyme neutralizing activity

Statistical Methods:

The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial. Any hypothesis tests will be 2-sided and will be viewed as exploratory. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical

variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time, as appropriate.

Unless otherwise indicated, all summary statistics will be presented by treatment group (either Q2W or Q4W) to which the patients were randomly assigned (patients who were initially assigned to Q2W or Q4W group in Study HGT-SAN-093 or patients who received no-treatment in Study HGT-SAN-093 and were randomly assigned to Q2W or Q4W in Study SHP-610-201). Additional analyses in the subgroup of patients who received no-treatment in Study HGT-SAN-093 may be performed.

All safety data will be summarized descriptively. The change from baseline at each time point for efficacy outcomes will be summarized. Generally, the mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented. Additional efficacy analyses in the subgroups of patients previously treated and untreated in Study HGT-SAN-093 may be performed.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis. The data included for treated patients in HGT-SAN-093 starts from the baseline of Study HGT-SAN-093 and for patients who received no-treatment in HGT-SAN-093 from the baseline of Study SHP-610-201. Baseline is the assessment obtained during the initial study period, prior to the first dose of HGT-1410, regardless of whether this occurred in Study HGT-SAN-093 or SHP-610-201.
Date of Original Protocol: 23 September 2014

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AEs	adverse events
ALB	albumin
ALK-P	alkaline phosphatase
ALT; SGPT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST; SGOT	asparate aminotransferase
AUC	area under the serum concentration-time curve
BBB	blood brain barrier
BSID-III	Bayley Scales of Infant and Toddler Development, 3rd Edition
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CK	creatine kinase
CL	clearance
Cl	chloride
C_{max}	maximum observed serum concentration
CNS	central nervous system
CO_2	carbon dioxide
con meds	concomitant medications
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
DMC	Data Monitoring Committee
DQ	developmental quotient
DS	dermatan sulfate
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FT	full-time
GAG	glycosaminoglycans
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hct	hematocrit
HCUQ	Healthcare Utilization Questionnaire
Hgb	hemoglobin
HNS	heparan N-sulfatase

Abbreviation	Definition
HS	heparan sulfate
ICH	International Conference on Harmonisation
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
IT	intrathecally
ITQoL	Infant Toddler Quality of Life Questionnaire™
ITT	Intent-to-Treat
IV	intravenously
K	potassium
KABC-II	Kaufman Assessment Battery for Children, 2nd Edition
LDH	lactate dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPS IIIA	Mucopolysaccharidosis Type IIIA or Sanfilippo Syndrome Type A
MRI	magnetic resonance imaging
NA	sodium
NCS	not clinically significant
NW	not working
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetics
PT	part-time
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
RBC	red blood cell
rhHNS	recombinant human heparan N sulfatase
SAE	serious adverse event
SAP	statistical analysis plan
SGSH	sulfoglucosamine sulfohydrolase
SI	Standard International
SOC	System Organ Class
$t_{1/2}$	terminal half-life
T_{max}	time of maximum observed serum concentration

Abbreviation	Definition
UADE	unanticipated adverse device effect
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
$V_{z/F}$	volume of distribution
WBC	white blood cell
WHO-DD	World Health Organization-Drug Dictionary
λ_Z	terminal rate constant

1 INTRODUCTION

Mucopolysaccharidosis Type IIIA (MPS IIIA, also called Sanfilippo Syndrome Type A) is a rare, autosomal recessive, lysosomal storage disease (LSD) presenting in early childhood that causes progressive neurodegeneration associated with intractable behavioral problems and developmental regression. Ultimately, a vegetative state supervenes. Life span is shortened, with death usually occurring in the late teen years. The genetic defect in this disorder is a mutation in both copies of the sulfoglucosamine sulfohydrolase (SGSH) gene, located on chromosome 17, which encodes the lysosomal enzyme, sulfoglucosamine sulfohydrolase, also called heparan-N-sulfatase, or sulfamidase. This enzyme is necessary for the normal intralysosomal catabolism of the glycosaminoglycan (GAG) (formerly termed mucopolysaccharide), heparan sulfate (HS). SGSH deficiency therefore results in the accumulation of heparan sulfate in lysosomes. Although the metabolic defect is expressed in every organ, the clinical manifestations of disease are primarily neurological. These are not usually apparent until 1 to 4 years of age. The molecular events linking the primary metabolic defect to the consequent neuropathology are not understood.

MPS III is the most prevalent of the mucopolysaccharidoses, and consists of 4 subtypes, A, B, C, and D.[1] Each of these is characterized by a deficiency of a distinct lysosomal enzyme necessary for the degradation of heparan sulfate. Clinically, on an individual patient level, the 4 subtypes cannot be reliably distinguished. Globally, subtype A is the most prevalent, at approximately 1 case in 100,000 live births, followed by subtype B, at approximately 1 in 250,000 live births.[1-3] Among MPS IIIA patients, there is wide allelic heterogeneity, with at least 100 SGSH mutations described to date. Most of these are missense, but nonsense mutations, deletions, insertions and splice-site mutations also occur.[4]

MPS IIIA symptoms usually arise in the 1st or 2nd year of life, although diagnosis is delayed until an average age of 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors that include aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5-7] There are also reports of unexplained, recurrent and severe diarrhea.[6] Overall, individuals with MPS IIIA exhibit progressive dementia with ultimate inanition and death resulting from the CNS disease. Lifespan is severely curtailed, with usual survival into the late teens.[6] Milder variants are recognized, with slower progression and survival to later age. The latter has been reported in approximately 10% of German patients with MPS IIIA, in association with the presence of the S298P mutation.[8]

No effective, disease-modifying therapies are currently approved as treatments for this devastating and disabling disease. A goal of Shire is to develop recombinant human heparan-N-sulfatase (rhHNS, development name HGT-1410) as enzyme replacement therapy (ERT) for patients with MPS IIIA. A particular problem for lysosomal storage disorders that damage the brain, such as MPS III, is how to target ERT to the brain, as macromolecules cannot cross the blood brain barrier (BBB).[9] In animal studies, ERT has been administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV) it does not cross the BBB after the immediate postnatal period of life. HGT-1410 has been

shown to be ineffective if administered intravenously in the MPS IIIA mouse model, in contrast to its efficacy in treating CNS pathology when administered into the CSF.[10]

In order to traverse the blood-brain barrier, HGT-1410 will be administered directly to the CNS using an intrathecal drug delivery device (IDDD) or, if the IDDD is non-functional, via lumbar puncture (LP). The advantage of using an IDDD is the potential to obviate the need for multiple lumbar punctures for drug delivery. HGT-1410 will be administered through the IDDD or, if the IDDD is non-functional, via lumbar puncture.

Please refer to the current edition of the Investigator's Brochure for further information concerning the nonclinical studies completed, including safety and clinical development of HGT-1410.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate long-term safety in patients with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo Type A) who received HGT-1410.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- The long-term cognitive function as measured by the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) or Kaufman Assessment Battery for Children, 2nd Edition (KABC-II), age-equivalent and developmental quotient (DQ) scores in patients with MPS IIIA who received HGT-1410
- The long-term adaptive behavioral function, assessed by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) in patients who received HGT-1410
- The total cortical grey matter volume, as assessed by volumetric magnetic resonance imaging (MRI) of the brain, in patients who received HGT-1410

2.3 Exploratory Objective

The exploratory objective of this study is [redacted]

2.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic and pharmacodynamics objectives of this study are to evaluate:

- The pharmacokinetics (PK) of HGT-1410 in serum
- The PK of HGT-1410 in CSF, in patients who received no-treatment in Study HGT-SAN-093
- The concentration of GAG in CSF and urine in patients who received HGT-1410

2.5 Health Status Objective

The health status objective of this study is to evaluate health status as measured by the Infant Toddler Quality of Life Questionnaire™ (ITQoL) instrument in patients who received HGT-1410.

2.6 Health Economics and Outcome Research Objective

The health economics and outcome research objective of this study is to evaluate healthcare resource utilization, as evaluated by the Healthcare Utilization Questionnaire (HCUQ), in patients who received HGT-1410.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

Safety is the primary objective of the study and will be assessed during the study by the following:

- collection of adverse events (by type, severity, and relationship to treatment [HGT-1410, the IDDD, device surgical procedure, or IT administration process])
- changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- physical examination
- vital signs
- 12-lead electrocardiogram (ECG) recordings
- CSF laboratory parameters (including chemistries, cell counts)
- anti-rhHNS antibodies in CSF and serum, including determination of antibodies having enzyme neutralizing activity

3.2 Secondary Endpoints

The secondary endpoints of this study are:

- The change from Baseline in BSID-III or KABC-II age-equivalent, DQ, and developmental delay scores
- The change from Baseline in adaptive behavioral function domains, assessed by VABS II, using raw scores, age-equivalent scores, and DQ scores
- The change from Baseline in total cortical grey matter volume, as assessed by MRI

3.3 Exploratory Endpoint(s)

[redacted]

3.4 Pharmacokinetic and Pharmacodynamic Endpoints

The pharmacokinetic endpoint is to determine the pharmacokinetic behavior of HGT-1410 in serum, based on the following parameters:

- Maximum observed serum concentration (C_{max})
- Time of C_{max} (T_{max})
- Area under the serum concentration-time curve from time zero to the last sampling time at which serum concentrations were measurable ($AUC_{0\text{-last}}$)
- Area under the serum concentration-time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Apparent terminal rate constant (λ_Z) derived from the slope of the log-linear regression of the log-linear terminal portion of the serum concentration-time curve.
- Terminal half-life ($t_{½}$) calculated as $0.693/ \lambda_Z$

- Clearance for IT-L administration ($CL/_F$)
- Volume of distribution based on the terminal phase for IT-L administration ($V_Z/_F$)

The pharmacodynamic endpoint is to determine the GAG concentrations in CSF and urine.

3.5 Health Status Endpoint

The health status endpoint is the Infant Toddler Quality of Life™ (ITQoL) scores at each assessment time and the corresponding change from Baseline.

3.6 Health Economics and Outcomes Research Endpoint

The health economic and outcome research endpoints evaluate the key HCUQ variables, such as the number of emergency room visits, caregiver employment status (full-time [FT], part-time [PT], and not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label extension study of HGT-1410 for patients who completed through at least the Week 48 Visit in Study HGT-SAN-093. The study design is presented in Figure 1. Patients who originally received HGT-1410 in Study HGT-SAN-093 will remain on the same dosing regimen as they received in Study HGT-SAN-093; Group 1 will receive HGT-1410 Q2W and Group 2 will received HGT-1410 Q4W. Patients in Groups 1 and 2 will begin treatment at Week 50 and Week 52, respectively, of this extension study (Study SHP-610-201). Patients who originally received no-treatment in Study HGT-SAN-093 (Group 3) will receive an IDDD following informed consent and will be re-randomized in a 1:1 allocation ratio to receive HGT-1410 via a Q2W or Q4W dosing regimen (Groups 3A and 3B, respectively) in Study SHP-610-201. Patients in Groups 3A and 3B will begin treatment on Week 0 of the extension study.

It is anticipated that the IDDD will be used to collect CSF samples and to deliver IT injections of HGT-1410 and preservative-free saline flushes. No other medication will be administered through the device. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual, which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug 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. General anesthesia or sedation may be required for injections of study drug and some evaluations, and may be used at the discretion of the Investigator. The Data Monitoring Committee (DMC) will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter (refer to Section 11.8).

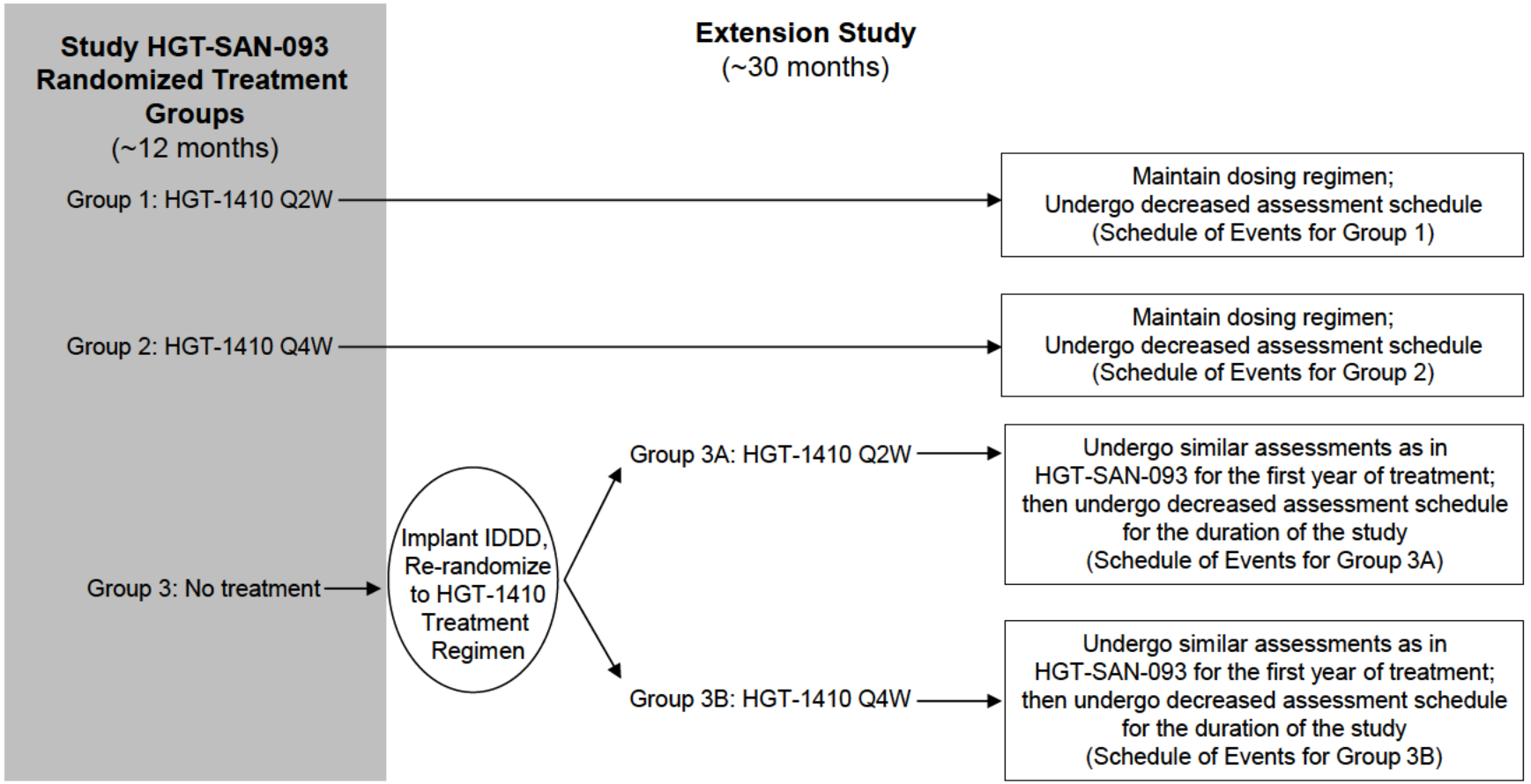
Patients will have the IDDD removed when they discontinue from or complete the study unless the patient is continuing to receive product or treatment through another mechanism (eg, extension study, expanded access program, commercially available drug).

Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of the extension study. A PK sample for patients who received HGT-1410 in Study HGT-SAN-093 will be obtained at the Week 96 visit (after approximately 2 full years of exposure to HGT-1410 across Studies HGT-SAN-093 and SHP-610-201). Serum PK samples for patients who received no-treatment in Study HGT-SAN-093 will be obtained at the Week 0, 48, and 96, and CSF PK samples will be obtained on the Week 0 and 48 visits in Study SHP-610-201.

Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no-treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

See Appendix 1 ,Appendix 2 ,Appendix 3, and Appendix 4 for the Study Schedule of Events Tables for Groups 1, 2, 3A and 3B, respectively.

Figure 1 SHP-610-201 Study Design



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

The study design is intended to provide ongoing treatment with HGT-1410 to patients who received HGT-1410 in Study HGT-SAN-093 and to initiate treatment to patients who received no-treatment in Study HGT-SAN-093. As such, all patients will be treated during this study; there is no control group.

In order to traverse the blood-brain barrier, HGT-1410 will be administered directly to the CNS using an IDDD or, if the IDDD is non-functional, via LP. The advantage of using an IDDD is the potential to obviate the need for multiple lumbar punctures for drug delivery. HGT-1410 will be administered through the IDDD or, if the IDDD is non-functional, via lumbar puncture.

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

4.3 Study Duration

Patients are expected to participate in this study for up to 30 months. Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no-treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

5 STUDY POPULATION SELECTION

5.1 Study Population

A maximum of 18 patients with MPS IIIA who completed Study HGT-SAN-093 are planned to enroll in this study.

5.2 Inclusion Criteria

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

1. Patient has completed through at least the Week 48 visit of Study HGT-SAN-093.
2. The patient's parent(s) or legally authorized guardian(s) has voluntarily signed an Institutional Review Board- (IRB-)/Independent Ethics Committee- (IEC-) approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

5.3 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria are met:

1. The patient, if randomized to treatment in Study HGT-SAN-093, has experienced a decline of more than 20 points in the BSID-III cognitive DQ score between Baseline and the Week 48 visit in Study HGT-SAN-093, AND, upon individual evaluation by the Investigator, has been deemed a treatment failure.
2. The patient has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with HGT-1410, including but not limited to clinically relevant intracranial hypertension, severe infusion-related reactions after treatment with HGT-1410, uncontrollable seizure disorder.
3. The patient has a known hypersensitivity to any of the components of HGT-1410.
4. The patient is enrolled in another clinical study, other than HGT-SAN-093, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT ® Mini S IDDD Instructions for Use, including:

The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT ® Mini S device

   a 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
   b The patient's drug therapy requires substances known to be incompatible with the materials of construction

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

7. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations, or is otherwise unlikely to complete the study) as determined by the Investigator.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Investigational Product

The investigational product to be used in this study is HGT-1410, recombinant human heparan N-sulfatase (rhHNS) for IT use.

The HGT-1410 drug product is a sterile solution for injection in single-use vials for IT administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, 0.02% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.

6.1.2 Intrathecal Drug Delivery Device

The drug product will be administered via the SOPH-A-PORT ® Mini S Implantable Access Port. The SOPH-A-PORT ® Mini S device is intended for long-term, intermittent access to the IT space for the delivery of investigational drug. The device is CE Marked in the European Union (EU) and investigational in non-EU countries.

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 SOPH-A-PORT ® Mini S Instructions for Use.

6.1.3 Comparator Product

Not applicable

6.2 Treatment Administered

The study drug will be administered through an IDDD. In the event of IDDD malfunction or failure, HGT-1410 may be administered via LP.

Patients who were randomized to receive HGT-1410 in Study HGT-SAN-093 will continue to have HGT-1410 administered through the IDDD that was implanted during Study HGT-SAN-093.

Patients who were randomized to no-treatment in Study HGT-SAN-093 will be scheduled to undergo surgical placement of the SOPH-A-PORT ® Mini S device. The initial implantation and any revision and/or explantation of the SOPH-A-PORT ® Mini S will be performed by pediatric

or general neurosurgeons or anesthesiologists who have experience in port and catheter implant procedures and intrathecal-access procedures and have completed training for the SOPH-A-PORT ® Mini S. Please refer to the IFU for further details. At least 7 days will be allowed for recovery following the placement of the IDDD before the administration of the first intrathecal dose of HGT-1410. During this time, the patient will receive standard perioperative care.

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

6.3 Selection and Timing of Dose for Each Patient

After meeting eligibility criteria, patients in Groups 1 and 2 (who received HGT-1410 in Study HGT-SAN-093) will begin treatment at Week 50 and 52, respectively, in Study SHP-610-201. Patients will be treated for up to 120 weeks in Study SHP-610-201, for a total cumulative exposure of 168 weeks across Studies HGT-SAN-093 and SHP-610-201.

After meeting eligibility criteria, patients who were randomized to no-treatment in Study HGT-SAN-093 will be scheduled to undergo surgical placement of the SOPH-A-PORT ® Mini S device, as described in Section 6.2. Thereafter, these patients will be administered HGT-1410 45 mg as an IT injection either Q2W or Q4W (Groups 3A or 3B, respectively), as randomized, for up to 120 weeks.

6.3.1 Missed Doses

Patients who are scheduled to receive Q2W dosing (Groups 1 and 3A) should receive their dose of HGT-1410 every 14 ± 3 days, and patients who are scheduled to receive Q4W dosing (Groups 2 and 3B) should receive their dose of HGT-1410 every 28 ± 7 days. If dosing cannot be administered within the indicated time window, the dose will be considered missed, and the patient will resume their dosing schedule with the next dose of HGT-1410. The dosing schedule will not change or be reset.

6.4 Method of Assigning Patients to Treatment Groups

Patients who were randomized to no-treatment in Study HGT-SAN-093 (Group 3) will be re-randomized in a 1:1 allocation ratio to receive Q2W or Q4W dosing (Groups 3A or 3B, respectively). To help ensure balance between the dose groups with respect to age at Baseline, the randomization will be stratified by age group (≤30 months and >30 months). (Refer to Section 10.3).

Patients who were randomized to receive HGT-1410 in Study HGT-SAN-093 will remain on the same treatment regimen in Study SHP-610-201.

6.5 Blinding

This study will not be blinded.

6.6 Prior and Concomitant Medications, Therapies, and Medical/Surgical Interventions

Prior and/or concomitant therapy prohibited for all patients in this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results.
- The use of medications which, in the opinion of the investigator, place patients at risk of bleeding complications following surgery or LP.
- Any other investigational therapy (drug or device) at any time during the study.
- Hematopoietic stem cell or bone marrow transplant.

6.7 Restrictions

6.7.1 Fluid and Food Intake

Not applicable

6.7.2 Patient Activity Restrictions

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

6.8 Treatment Compliance

Treatment with HGT-1410 will be administered via an IDDD under the supervision of the investigator and in the controlled environment of a clinical center; therefore, full patient compliance with treatment is anticipated in this study.

6.9 Packaging and Labeling

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

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 and will be in accordance with local regulatory requirements.

6.10 Storage and Accountability

6.10.1 Investigational Product

HGT-1410 will be supplied at a concentration of 15 mg/mL in single-use vials for IT administration.

HGT-1410 will be shipped by Shire or a qualified distributor to the clinical study site(s) at 2 to 8°C (36 to 46 °F).

Drug product should be stored refrigerated (2 to 8°C); drug product may not be used beyond the expiration date on the vial.

The disposition of all investigational product delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the clinical trial material accountability log. The date and time of administration of the investigational 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 product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

The process for destruction of investigational product is provided in the Pharmacy Manual.

See the Pharmacy Manual for additional details.

6.10.2 Intrathecal Drug Delivery Device

The disposition of all SOPH-A-PORT ® Mini S devices delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the Accountability Log. The date and time of administration of the investigational product and use of the SOPH-A-PORT ® Mini S device must be documented on the 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 devices and return of used/unused SOPH-A-PORT ® Mini S device(s) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT ® Mini S devices are available for the monitor to inventory and prepare for product destruction or return shipment to the Sponsor or designee.

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

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

6.10.3 Comparator Product

Not applicable to this study.

7 STUDY PROCEDURES

Detailed descriptions of patient procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events for Group 1 (patients who received HGT-1410 Q2W in Study HGT-SAN-093) in Appendix 1, for Group 2 (patients who received HGT-1410 Q4W in Study HGT-SAN-093 in Appendix 2, for Group 3A (patients who received no-treatment in Study HGT-SAN-093 and are randomized to receive HGT-1410 Q2W in Study SHP-610-201) in Appendix 3, and for Group 3B (patients who received no-treatment in Study HGT-SAN-093 and are randomized to receive HGT-1410 Q4W in Study SHP-610-201) in Appendix 4.

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

Details for sample collection are described in the Laboratory Manual for Study SHP-610-201.

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).

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 and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria

Each patient in Groups 1 and 2 (those who received HGT-1410 in Study HGT-SAN-093) will be reviewed for eligibility against the study entrance criteria prior to receiving HGT-1410 on Week 50 and 52, respectively.

All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

Each patient who received no-treatment in Study HGT-SAN-093 (Group 3) will be reviewed for eligibility against the study entrance criteria before IDDD implantation.

Patients who do not 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.

7.3 Hearing and Vision Assessments

7.3.1 Investigator Assessment of Hearing and Vision

For patients who received no-treatment in Study HGT-SAN-093 (Group 3) only, the Investigator will use their clinical judgment to assess the patient's vision during the initial physical examination. Investigator judgment will be used to determine whether the patient's hearing and vision is adequate for cooperation with neurodevelopmental testing, as indicated in the study inclusion criteria.

7.4 Device Related Study Procedures

7.4.1 IDDD Implantation or Revision Procedures

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

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

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

7.4.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative x-ray check of the IDDD will be performed following surgery for Groups 3A and 3B to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, as needed, throughout the study. At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional x-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray will be performed to assess the potential cause of malfunction. Fluoroscopy should be used during device implantation procedures.

7.4.3 CSF Sampling Procedure

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

7.4.4 Device Revision or Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage using the standard administration steps detailed in the device's IFU due to a device-related issue, the

IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

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

Details of the device removal will be recorded in the patient's electronic case report form (eCRF). Refer to the SOPH-A-PORT ® Mini S IFU for further details.

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, extension study, expanded access program, commercially available drug).

7.5 Investigational Product Administration

Patients will be administered HGT-1410 IT by means of an IDDD, either every 2 weeks or every 4 weeks. 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 4 hours post-dosing and will be discharged when deemed clinically stable by the Investigator. The number of IDDD revisions/ replacements is limited to 2 per patient in any 6-month period. Therefore, in the "worst case scenario" of 2 IDDD failures occurring within 1 month, up to 11 consecutive doses of HGT-1410 administered via LP will be necessary for patients in the Q2W dosing group, and up to 5 consecutive doses via LP will be necessary for patients in the Q4Wdosing group until the IDDD can be revised or replaced.

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

It is expected that all or most doses of HGT-1410 will be successfully administered following the application of topical anesthetic cream to the skin overlying the IDDD access port (see IDDD Manual for details). However, in some cases, sedation or general anesthesia may be required, and may be used at the discretion of the Investigator. Any sedative or anesthetic drugs used must be recorded as concomitant medications.

Intrathecal administration of investigational product will be preceded by CSF sampling for clinical laboratory analysis (cell count, protein, glucose), and storage for additional analyses which may include: PD (GAG concentration), analyses of HGT-1410 enzyme and anti-rhHNS antibodies, according to the relevant Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

All HGT-1410 administrations will be followed by a flush with preservative-free saline of at least 2 mL. The total volume of investigational product and flush administered is targeted towards replenishing the volume of CSF withdrawn. If the total volume of HGT-1410 plus 2 mL saline flush is less than the total volume of CSF withdrawn, additional saline will be administered to balance the volumes withdrawn and injected.

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

7.6 Efficacy Assessments

7.6.1 Neurocognitive and Developmental Assessments

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of patient neurodevelopmental status (see Table 7-1).[11] The assessments are estimated to last between 2 and 4 hours and must be conducted prior to any invasive procedures, such as blood draws, and prior to sedation or anesthesia. Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows:

- Cognition: the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)[12] will be used to assess all patients through the age of 42 months. Once patients reach 42 months chronological age, an attempt will be made to switch the cognitive assessment to the Kaufman Assessment Battery for Children-Second Edition (KABC-II). If the cognitive status of the patient does not allow for testing by the KABC-II, the BSID-III may be used.
- Adaptive behaviors: the Vineland Adaptive Behavioral Scales, Second Edition (VABS II)[13] will be used to assess all patients.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments are summarized below in Table 7-1.

Table 7-1 Neurodevelopmental Assessments Tests

Cognitive Test or Scale	Developmental or Cognitive Areas of Assessment
Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)[12]	Summary score and sub-domains: - Cognitive - Motor - Social/Emotional - Language
Kaufman Assessment Battery for Children, Second Edition (KABC-II)	Cognitive and processing skills
ADAPTIVE BEHAVIOR	
Vineland Adaptive Behavior Scales, Second Edition (VABS II)[13]	Communication Daily Living Socialization Motor Skills

7.6.2 Quality of Life Indicator: Infant Toddler Quality of Life Questionnaire

The Infant Toddler Quality of Life Questionnaire™ (ITQoL) will be administered during the study. The ITQoL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social wellbeing of the child and assesses the quality of the parent/guardian's life. If a patient is over 5 years of age, they do not have to complete the ITQoL.

7.6.3 Health Economics and Outcomes Research: Healthcare Utilization Questionnaire

The Healthcare Utilization Questionnaire (HCUQ) will be administered during the study. This HCUQ focuses on the direct and indirect costs of care for patients with MPS-III.

7.7 Magnetic Resonance Imaging

7.7.1 Head

Regional brain volumes, including total cortical gray matter volume, will be assessed through an MRI of the head. The patient will be under general anesthesia for this assessment. Instrument standardization and central analysis of MRIs will be performed by a designated contract research laboratory.

7.7.2 Liver and Spleen

Liver and spleen volumes will be assessed through an MRI, performed at the same times as for the MRI of the head. The patient will be under general anesthesia for this assessment. Instrument standardization and central analysis of MRIs will be performed by a designated contract research laboratory.

7.8 Pharmacokinetic Assessments

Blood samples will be collected for measurement of serum concentrations of HGT-1410 and determination of PK parameters at the times specified in Schedules of Events (Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 5). Additionally CSF samples will be collected from patients who received no-treatment in Study HGT-SAN-093 at the times specified in the Schedules of Events (Appendix 3, Appendix 4, and Appendix 5). The results of these assessments will be addressed in a separate PK report.

Patients may be discharged from the hospital after the 24-hour blood draw. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); this will be decided in consultation with the Investigator. Patients will return to the hospital for PK blood and CSF sampling at the 48-hour time point. Patients will be discharged to home after the physical examination and blood draws have been completed at the 48-hour PK time point. See Appendix 5 for more details regarding timing for PK sample collection.

Serum and CSF PK collection, processing, and shipping instructions will be provided in the Laboratory Operations Manual.

7.9 Pharmacodynamic Biomarker Assessments (CSF and Urine GAG Levels)

CSF and urine samples will be obtained to measure the concentration of GAG according to the schedules of events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4). Details about CSF collection are provided in Section 7.11.5.3.

7.10 Concomitant Medications, Therapies, and Medical/Surgical Interventions

All non-protocol treatments and medications that occur from the time of informed consent through the safety follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the eCRF. Concomitant therapy includes any therapies/interventions administered to patients, and these will be recorded on the concomitant therapy eCRF. Any medical/surgical procedures performed on the patients will be recorded on the concomitant medical/surgical procedures eCRF. Concomitant medications, both prescribed and over-the-counter (including genistein and anesthesia medications) will be recorded on the concomitant medication eCRF.

Every effort should be made to keep symptomatic MPS IIIA treatment constant throughout the study. However, changes in medications are acceptable if necessary according to clinical judgment. All changes will be recorded on the appropriate eCRF. Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

7.11 Safety Assessments

7.11.1 Vital Signs

Vital signs are to be recorded on the eCRF for all patients and will include heart rate, blood pressure, respiration rate, and body temperature. Vital signs will be recorded for at least 4 hours following each dose of HGT-1410, as described in the Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

7.11.2 Physical Examination, including Height, Weight, and Head Circumference

During the study, physical examinations will be performed at the time points indicated in the SOEs. For Groups 1 and 2, full physical examinations will be conducted at Weeks 96, 120, 144, and 168, and for Groups 3A and 3B, full physical examinations will be conducted during the IDDD implantation period and at Weeks 24, 48, 72, 96, and 120. The remainder of physical examinations will be symptom-directed.

Physical examinations will include a review of the patient's general appearance, neurological examination, as well as evaluation of the body systems described in Table 7-2, including the port and catheter track. Any abnormal change in findings will be recorded as an AE on the appropriate eCRF.

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
General appearance	Endocrine
Head and neck	Cardiovascular

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
Eyes	Abdomen
Ears	Genitourinary
Nose	Skin
Throat	Musculoskeletal
Chest and lungs	Neurological
Port and catheter track	

Height and weight will be recorded for all patients.

The clinical site staff will be instructed to use calibrated scales for weight measurement where possible. The same scale is to be used at the clinical site for all patients at each specified time point during the study.

Head circumference will be measured for Groups 3A and 3B during the IDDD implantation period. All data will be recorded on the eCRF.

7.11.3 Electrocardiogram

An ECG will be performed in accordance with the clinical site's standard practice(s) and are to be performed after study drug administration. Electrocardiogram recordings will be read locally at the clinical site and will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, and QT. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF. If the patient is unable to cooperate with electrocardiography, and if sedation or general anesthesia is employed during that study visit, the ECG may be performed under sedation / anesthesia.

7.11.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection. Procedures for collection and handling of samples are included in the Laboratory Manual.

Clinical laboratory tests will include the following (See Table 7-3):

Table 7-3 List of Laboratory Tests

Hematology:

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

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Microscopic examination
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen
- Triglycerides
- Uric acid

Anti-rhHNS antibody assessment

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Creatine kinase (CK) and subtypes
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Coagulation (performed at IDDD implantation):

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

7.11.5 Cerebrospinal Fluid Assessments

Cerebrospinal fluid will be obtained from patients during surgical implantation of the IDDD (Groups 3A and 3B only), immediately prior to each injection of study drug, and at the safety follow-up visit. Should the IDDD become clogged or undergo mechanical complications, the CSF sample will be obtained via LP.

The volume of CSF collected at each visit will vary according to the number of CSF assessments. The initial 1 mL of CSF aspirated via the IDDD will be discarded, to eliminate fluid in the device “dead space”. The next 1 mL of CSF will be sent to the local laboratory. Subsequently drawn CSF will be stored, depending on the requirement for that visit (refer to the schedules of events in Appendix 1, Appendix 2, Appendix 3 Appendix 4 and the Laboratory ory Manual). If CSF is obtained via lumbar puncture, there is no need to discard the first mL of CSF, and this can be sent to the local laboratory for standard clinical assessments. If the patient

is clinically stable in the opinion of the investigator, HGT-1410 can be administered immediately following withdrawal of CSF, without awaiting the results of the CSF clinical laboratory data.

Each CSF sample collected will have the assessments described in Sections 7.11.5.1 through 7.11.5.4. Cerebrospinal fluid sample collection, processing, and shipping instructions are provided in the Laboratory Manual.

7.11.5.1 Standard CSF Safety Laboratory Assessments

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

7.11.5.2 Anti-rhHNS Antibodies and Biomarkers in CSF

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of Anti-rhHNS antibody evaluation, exploratory proteomics biomarkers, and/or other CSF biomarkers.

7.11.5.3 CSF GAG Levels and Biomarkers

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of CSF GAG, GAG degradation components, HS/dermatan sulfate (DS) oligosaccharides, or other CSF markers. The CSF PD sample will be obtained at the same visit as a serum sample as described in Section 7.9.

7.11.5.4 [redacted]

[redacted]

7.11.6 Device Assessments

[redacted]. These data will be collected on the patient's eCRF from the time of initial implantation.

7.11.7 Collection and Storage of Biological Samples for Biomarker Studies

Biomarker analyses may be performed at the Shire research laboratory or at a Shire-designated research laboratory. Collection and processing of CSF samples will be performed as specified in the Laboratory Manual. Samples will be stored securely to ensure patient confidentiality. Samples obtained for this study will be stored for up to 10 years. Thereafter, samples will be destroyed.

7.12 Sample Collection, Storage, and Shipping

Details for study procedures including sample collection are provided in the Laboratory Manual for this study.

7.13 Adverse Events Assessments

7.13.1 Definitions of Adverse Events and Serious Adverse Events

7.13.1.1 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 product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- 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 eCRF, regardless of the severity or relationship to investigational product. 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.

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.

7.13.1.2 Adverse Events Due to Systemic Exposure to HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration. Investigators will judge the relationship of AEs to the drug infusion and describe the clinical details on the AE form. The temporal relationship of an AE to the drug infusion will be determined upon analysis of the AE and study treatment administration data.

7.13.1.3 IDDD-related Adverse Events

IDDD ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site or subcutaneous tract infection. A malfunction of the device (defined in Section 7.13.2.2) should not be entered as an adverse event unless it has physiological consequences. In the event of a device failure (defined in Section 7.13.2.3), the device may need to be replaced or repaired. If overnight hospitalization is required for such a procedure (or the device failure meets any other serious criteria, eg, medically important), the device failure will be reported as a serious adverse event. Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF and the serious adverse event (SAE) form (when applicable). A list of the most common IDDD AEs is included in Appendix 6.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS (FOR IT STUDIES; AMEND/DELETE SECTION AS APPLICABLE)

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 relat4ed to the surgical procedure itself.

IT ADMINISTRATION PROCESS ADVERSE EVENTS

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

7.13.1.4 Serious Adverse Event

1. An SAE is any AE occurring at any dose of investigational drug or procedure that results in any of the following outcomes:
   - Death
   - Is life-threatening
   - Requires hospitalization
   - Requires prolongation of existing hospitalization
   - A persistent or significant disability or incapacity
   - A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered 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).

2. Unanticipated Adverse Device Effect (UADE) - 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).

7.13.2 Device-associated Definitions

7.13.2.1 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.

7.13.2.2 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.

7.13.2.3 Device Failure

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

7.13.3 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-4. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-4 Adverse Event Severity

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

7.13.4 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.

7.13.5 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product, device (IDDD), device surgical procedure, or IT administration process will be assessed by the Investigator based on the following definitions (See Table 7-5).

Table 7-5 Adverse Event Relatedness

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

7.13.6 Procedures for Recording and Reporting Adverse Events

7.13.6.1 Adverse Event Monitoring and Period of Observation

Adverse events (AEs) 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, the patient's parent(s), or the patient's legally authorized representative 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 30 days after the last dose for patients who complete the study.

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.

7.13.6.2 Reporting Serious Adverse Events

Any SAE, regardless of relationship to investigational 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 product and/or device. 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:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] **(UK) OR United States FAX:** [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted]**, MD**

Email: [redacted]

FAX: [redacted] **(USA)**

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

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

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

The Investigator must promptly report all required information to the IRB/IEC. It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/ MedWatch 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.

7.14 Abuse, Overdose and Medication Error

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

Misuse – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: 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 medicinal product higher than the protocol-mandated dose. No clinical information on overdose is available.

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

All investigational medicinal product provided to pediatrics should be supervised by the parent/legally-authorized representative/caregiver.

7.15 Removal of Patients from the Trial or Investigational 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 one or more study visits
- The patient was erroneously included in the study
- The patient develops an exclusion criterion

- The patient suffers an intolerable adverse event
- The study is terminated by the Sponsor

The patient, the patient's parent(s), or the patient's legally authorized representative 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 or the patient's parent(s) or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the safety follow-up assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. 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.

7.16 Safety-Related Study Stopping Rules

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

This study will be stopped and safety data reviewed if any patient experiences a life-threatening or fatal SAE, either of which is considered possibly or probably related to the investigational product.

Following the review of safety data, the status of the study will be one of the following:

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

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

7.17 Appropriateness of Measurements

The neurocognitive and developmental assessments planned for this study are intended to gauge the potential treatment effect and safety of 2 dose levels of HGT-1410 over time on behavioral and cognitive criteria in patients with MPS IIIA. The selection of tests used for the cognitive assessment, and the expression of results as a ratio of mental age equivalence to calendar age to generate a DQ, were developed in collaboration with clinical psychologists with expertise in the assessment of severely disabled children with neurometabolic diseases.

The BSID-III, KABC-II, and VABS II are instruments that have been used to assess development in healthy children and those with developmental delay. Their use in this study will contribute to their validation in patients with MPS IIIA. The utility of these measures to track

disease progression has been demonstrated in Shire's natural history study of MPS IIIA (HGT-SAN-053).

The BSID-III was selected for the following reasons:

- Widespread familiarity with the instrument
- Availability of age equivalent scores for severely impaired children
- Nonverbal content (ie, on the cognitive scale on the BSID-III)
- Availability of language and motor assessment (both are domains on the BSID-III).

The BSID-III is validated for children through the age of 42 months. Patients are to be switched to another instrument, the KABC-II, to measure cognition after the age of 42 months. The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

The VABS II, a parent-reported outcome, was selected as an adaptive measure for the same reasons. Of note, to maximize standardization and reduce bias, the "interview" form of the VABS II will be administered by the clinical psychologist/psychometrist at the same time as the BSID assessment.

The use of age equivalent scores rather than standard scores permits the assessment of children with severe disability in whom standard scores would otherwise be insensitive to change. Given the potentially rapid progression of MPS IIIA, a child who is assessable using a standard score at baseline may rapidly decline to such an extent that the assessment "floor" is reached and further change is not measurable. Additionally, the use of age equivalence scores permits comparison and correlation between the BSID-III and VABS II. The use of DQ yields a parameter that tracks the dynamic progression of MPS IIIA disease, as observed in Shire's natural history study.

This study will utilize standard safety assessments including; AEs, vital signs, standard clinical tests, and ECGs. Antibodies against the investigational drug will also be measured.

8 STUDY ACTIVITIES

The timing of study activities are described for each of the 3 patient groups below, and in Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively for Group 1 (initially randomized to receive HGT-1410 Q2W in Study HGT-SAN-093), Group 2 (initially randomized to receive HGT 1410 Q4W in Study HGT-SAN-093), Group 3A (initially randomized to no-treatment in Study HGT-SAN-093 and randomized to HGT-1410 Q2W in Study SHP-610-201), and Group 3B (initially randomized to no-treatment in Study HGT-SAN-093 and randomized to HGT-1410 Q4W in Study SHP-610-201). Study activities for all patients are detailed in Section 7.

8.1 Group 1 (Maintaining Q2W Dosing)

8.1.1 Treatment Period (Weeks 50 through 168)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 1 will receive 45 mg HGT-1410 IT Q2W (ie, every 14 ±3 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

The first 48 weeks of treatment for Group 1 occurred in Study HGT-SAN-093, and therefore patients in Group 1 will begin this study at Week 50.

For patients in Group 1, HGT-1410 will be administered every other week from Week 50 through Week 168.

8.1.1.1 Pre-treatment Assessments

- Review of study eligibility and informed consent
- Full physical examination, including height and weight at Weeks 72, 96, 120, 144, and 168. Symptom-directed physical examination at all other visits.
- Every visit: Vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive / Behavioral Assessments: BSID-III/KABS-II and VABS II: Weeks 72, 96, 120, 144, and 168.
- Quality of Life (QoL) questionnaire: ITQoL for patients ≤ 5 years of age: Weeks 72, 96, 120, 144, and 168
- Health economics questionnaire: HCUQ: Weeks 72, 96, 120, 144, and 168
- MRIs of head, liver, and spleen: Weeks 96 and 144
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit before dosing: Standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168

- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Serum PK sampling at Week 96 – see Appendix 5 for the PK collection schedule

8.1.1.2 Post-treatment Assessments

- ECG at Weeks 96, 144, and 168
- Serum PK sampling at Week 96 – see Appendix 5 for the PK collection schedule
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.1.2 Safety Follow-up Visit: Week 172 (±7 days)

All patients will have a safety follow-up at Week 172 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed physical examination
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.2 Group 2 (Maintaining Q4W Dosing)

8.2.1 Treatment Period (Weeks 52 through 168)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 2 will receive 45 mg HGT-1410 IT Q4W (ie, every 28 ±7 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

The first 48 weeks of treatment for Group 2 occurred in Study HGT-SAN-093, and therefore patients in Group 2 will begin this study at Week 52.

For patients in Group 2, HGT-1410-IT Q4W study drug will be administered Q4W from Week 52 through Week 168.

8.2.1.1 Pre-treatment Assessments

- Review of study eligibility and informed consent

- Full physical examination, including height and weight at Weeks 72, 96, 120, 144, and 168. Symptom-directed physical examination at all other visits.
- Every visit: Vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive / Behavioral Assessments: BSID-III/KABS-II and VABS II: Weeks 72, 96, 120, 144, and 168.
- QoL questionnaire: ITQoL for patients ≤ 5 years of age: Weeks 72, 96, 120, 144, and 168
- Health economics questionnaire: HCUQ: Weeks 72, 96, 120, 144, and 168
- MRIs of head, liver, and spleen: Weeks, 96 and 144
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit before dosing: Standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Serum PK sampling at Week 96 – see Appendix 5 for the PK collection schedule

8.2.1.2 Post-treatment Assessments

- ECG at Weeks 96, 144, and 168
- Serum PK sampling at Week 96 – see Appendix 5 for the PK collection schedule
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.2.2 Safety Follow-up Visit: Week 172 (±7 days)

All patients will have a safety follow-up at Week 172 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed physical examination
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.3 Group 3 (Patients who were randomized to no-treatment in Study HGT-SAN-093)

Patients in Group 3 received no-treatment in Study HGT-SAN-093, and therefore these patients will begin this study at Day -27 to -7.

8.3.1 IDDD Implantation (Days -21 to Day -7)

8.3.1.1 Prior to IDDD Implantation

Prior to enrollment in the study, patients who were initially randomized to no-treatment in Study HGT-SAN-093 will undergo the following assessments during the IDDD implantation period, prior to IDDD implantation surgery:

• Written informed consent • Assessment of eligibility according to inclusion/exclusion criteria • Vital signs • Investigator assessment of vision and hearing ability • Physical examination, including height, weight, and head circumference • ECG	• Clinical laboratory tests, including PT and aPTT • BSID-III/KABC-II • VABS II • ITQoL (for patients ≤ 5 years of age) • HCUQ • Concomitant medications, therapies, and procedures • AE monitoring

The physical examination, ECG, height, weight, and clinical labs (hematology, serum chemistry, and urinalysis) need to be performed within 7 days prior to the IDDD implantation surgery date. If more than 7 days elapse between the date of these assessments and the IDDD implantation surgery date, the assessments must be repeated within 7 days prior to surgery.

8.3.1.2 Day of IDDD Implantation

Surgical implantation of the IDDD includes surgical implantation of the IDDD and a post-surgical assessment. IDDD placement will require anesthesia.

Assessments to be performed on the day of IDDD implantation include:

Prior to anesthesia	During time patient is anesthetized
• Symptom-directed physical examination (PE) • ECG (before anesthesia if possible) • Vital signs • AE monitoring • Concomitant medications, therapies, and procedures	• If logistically possible, head, liver and spleen MRI (before IDDD implantation) • IDDD implantation • CSF samples collected for clinical laboratory analysis (chemistry, cell count), CSF GAG, CSF storage for biomarkers • Post Operative: X-ray to check IDDD placement

8.3.2 Post-operative Check - Days 1 to 3

The post-operative check can occur anytime 1-3 days after IDDD implantation. Assessments include: post-operative check of the IDDD incision, vital signs, symptom-directed physical examination, concomitant medications, therapies, and procedures, and AE monitoring.

8.3.3 Randomization (Can Occur Any Time After Meeting Study Entry Criteria)

All patients in Group 3 (patients who were initially randomized to no-treatment in Study HGT-SAN-093) will be randomized in a 1:1 allocation ratio to receive Q2W or Q4W dosing (Groups 3A or 3B, respectively), as described in Section 6.4.

8.4 Group 3A (Initiating HGT-1410 Q2W Dosing)

8.4.1 Treatment Period (Weeks 0 through 120)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 3A will receive 45 mg HGT-1410 IT Q2W (ie, every 14 ±3 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

For patients in Group 3A, HGT-1410 will be administered every other week from Week 0 through Week 120.

8.4.1.1 Pre-treatment Assessments

- Full physical examination, including height and weight at Weeks 24, 48, 72, 96, and 120. Symptom-directed physical examination at all other visits.
- Every visit: Vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive / Behavioral Assessments: BSID-III/KABS-II and VABS II: Weeks 24, 48, 72, 96, and 120
- QoL questionnaire: ITQoL for patients ≤ 5 years of age: Weeks 24, 48, 72, 96, and 120
- Health economics questionnaire: HCUQ: Weeks 24, 48, 72, 96, and 120
- MRIs of head, liver, and spleen: Weeks 24, 48, and 96
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Every study visit before dosing: Standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, and 120
- Every study visit: CSF sample collection for storage for biomarkers
- Anti- rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120

- Serum PK sampling at Weeks 0, 48, and 96 – see Appendix 5 for the PK collection schedule
- CSF PK sampling at Weeks 0 and 48 – see Appendix 5 for the PK collection schedule

8.4.1.2 Post-treatment Assessments

- ECG at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 96, and 120
- Serum PK sampling at Weeks 0, 48, and 96 – see Appendix 5 for the PK collection schedule
- CSF PK sampling at Weeks 0 and 48 – see Appendix 5 for the PK collection schedule
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.4.2 Safety Follow-up Visit: Week 124 (±7 days)

All patients will have a safety follow-up at Week 24 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed physical examination
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.5 Group 3B (Initiating HGT-1410 Q4W Dosing)

8.5.1 Treatment Period (Weeks 0 through 120)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 3B will receive 45 mg HGT-1410 IT Q4W (ie, every 28 ±7 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

For patients in Group 3B, HGT-1410 will be administered Q4W from Week 0 through Week 120.

8.5.1.1 Pre-treatment Assessments

- Full physical examination, including height and weight at Weeks 24, 48, 72, 96, and 120. Symptom-directed physical examination at all other visits.
- Every visit: Vital signs, concomitant medications, therapies, and procedures, and AE monitoring

- Cognitive / Behavioral Assessments: BSID-III/KABS-II and VABS II: Weeks 24, 48, 72, 96, and 120
- QoL questionnaire: ITQoL for patients ≤ 5 years of age: Weeks 24, 48, 72, 96, and 120
- Health economics questionnaire: HCUQ: Weeks 24, 48, 72, 96, and 120
- MRIs of head, liver, and spleen: Weeks 24, 48, and 96
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Every study visit before dosing: Standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, and 120
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Serum PK sampling at Weeks 0, 48, and 96 – see Appendix 5 for the PK collection schedule
- CSF PK sampling at Weeks 0 and 48 – see Appendix 5 for the PK collection schedule

8.5.1.2 Post-treatment Assessments

- ECG at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 96, and 120
- Serum PK sampling at Weeks 0, 48, and 96 – see Appendix 5 for the PK collection schedule
- CSF PK sampling at Weeks 0 and 48 – see Appendix 5 for the PK collection schedule
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.5.2 Safety Follow-up Visit: Week 124 (±7 days)

All patients will have a safety follow-up at Week 24 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed physical examination
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE 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. The training will be documented.

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 Food and Drug Administration (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 and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Statistical analysis will generally be performed by the Biometrics Department of Shire using SAS statistical software (SAS Institute, Cary, NC, USA). Analysis of any PK and health economics and outcomes data will be performed by the Shire Clinical Pharmacology and Pharmacokinetics group and the Health Economics and Outcomes Research groups, respectively. The analysis methods for all other study data (demographic and baseline characteristics, efficacy variables, and safety variables) will be detailed in the statistical analysis plan (SAP). The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial.

Any hypothesis tests will be 2-sided and will be viewed as exploratory. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

Unless otherwise indicated, all summary statistics will be presented by treatment group (either Q2W or Q4W) to which the patients were randomly assigned (for patients who were initially assigned to Q2W or Q4W group in Study HGT-SAN-093 or patients who were assigned to no-treatment in HGT-SAN-093 and were randomly assigned to Q2W or Q4W in Study SHP-601-201).

All safety data will be summarized descriptively. The change from baseline at each time point for efficacy outcomes will be summarized. Generally, the mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented. If the parametric assumption for the distribution cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference and the corresponding 95% confidence interval (ie, median difference or Hodges–Lehmann estimator and the corresponding confidence intervals). Developmental Quotients (DQ) will be computed as a ratio, expressed as a percentage using the age equivalent score divided by the age at testing (ie, [age equivalent score/chronological age] x 100). Developmental delay scores will be calculated as the age equivalent score minus the chronological age. Additional efficacy analyses in the subgroups of patients who received treatment or no-treatment in Study HGT-SAN-093 will be performed.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis. The data included for treated patients in HGT-SAN-093 starts from the baseline of Study HGT-SAN-093 and for patients who received no-treatment in HGT-SAN-093 from the baseline of Study SHP-610-201. Baseline is the assessment obtained prior to the first dose of HGT-1410.

10.2 Determination of Sample Size

As this is an extension study of Study HGT-SAN-093, any patients who enrolled and completed that study are eligible to enroll in Study SHP-601-201, and no statistical estimation for sample

size calculation was performed. A maximum sample size of 18 patients in this study is expected based on the sample size in Study HGT-SAN-093.

10.3 Method of Assigning Study Subjects to Treatment Groups

Patients who were randomized to receive Q2W or Q4W dosing in Study HGT-SAN-093 (Groups 1 and 2, respectively) will maintain their assigned dosing regimen in Study SHP-610-201.

Patients who were randomized to receive no-treatment in Study HGT-SAN-093 (Group 3) will be re-randomized in a 1:1 allocation ratio via a computer-generated randomization schedule to receive Q2W or Q4W dosing regimen (Groups 3A or 3B, respectively) in Study SHP-610-201. To help ensure balance between the dose groups with respect to age at Baseline, the randomization will be stratified by age group (≤30 months and >30 months).

10.4 Population Description and Exposure

10.4.1 Analysis Populations

The population for all safety analyses will be the Safety population, defined as all patients who had the IDDD implant or received at least one dose of study drug in the extension study. Safety analyses will be conducted according to the treatment received. Device related analyses will be conducted in the subset of patients in the Safety Population who had the device implanted.

The population for all efficacy analyses will be the Intent-to-Treat (ITT) population, defined as all randomized patient according to the treatment assigned.

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

10.4.2 Subject Disposition

The number of patients screened; the number and proportion of patients randomized, included in the Safety population, completed the study, and discontinued prematurely will be presented in a summary table by treatment group; reasons for discontinuation/withdrawal will also be summarized.

10.4.3 Protocol Deviations

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

10.4.4 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by the individual treatment group and the overall HGT-1410 treatment group for the Safety population.

10.4.5 Treatment Compliance and Extent of Exposure

The total number of doses of study drug, the number of doses received via IDDD, the number of doses received via LP, the average duration of IT administration and treatment compliance will be summarized by treatment group for the Safety population.

The duration of IT administration is calculated by subtracting the IT administration start time from the IT administration end time.

Treatment compliance is defined as: [(Number of Complete IT administrations) ÷ (Expected Number of IT administrations)] * 100.

10.5 Analysis of Efficacy

The analysis of efficacy data will be based on the ITT population.

10.5.1 Primary Analysis

The primary objective of this study is to evaluate long-term safety of HGT-1410 in patients with MPS-III. Therefore the primary analysis will be discussed in the safety analysis section, Section 10.7.

10.5.2 Secondary Efficacy Analysis

10.5.2.1 Bayley Scales of Infant Development III (BSID-III)/Kaufman Assessment Battery for Children-Second Edition (KABC-II)

The observed values and changes from baseline in DQ, age equivalent, and developmental delay scores for each subtest (Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross motor) will be summarized descriptively for each assessment time point by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean age equivalent and DQ scores for the subtests across time will be presented. A trellis plot of the age equivalent and DQ scores within each patient will be presented. Furthermore, a spaghetti plot of the cognitive age equivalent score against chronological age will be presented.

The KABC-II is an alternative to BSID-III. The KABC-II cognitive DQ, age-equivalent and developmental delay scores will be combined with the corresponding BSID-III scores and summarized at each assessment time point as described above. Most of the patients will have either only BSID-III data or KABC-II data. If a patient has data obtained by each of these methods, then the method for which data is available at both baseline and post-baseline time points will be used when combining the DQ scores and age-equivalent scores.

10.5.2.2 Vineland Adaptive Behavior Scales II (VABS II)

Tabular summaries of the raw scores for each domain, the average domain raw scores, the mean age equivalent score and the corresponding overall DQ scores and the corresponding change from baseline will be presented for each assessment time point by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean raw scores for the domains across time will be presented. In addition, a trellis plot of the raw scores within each patient will be presented. Similar plots will be presented for the average domain raw scores, the mean age equivalent score and the overall DQ score. A spaghetti plot of mean age equivalent score against chronological age will also be presented.

10.5.2.3 Brain MRI

Although several MRI parameters will be captured, the analysis will focus primarily on the grey matter volume, the white matter volume and the intracranial CSF volume (ventricles plus additional CSF space). The observed values and changes from baseline will be summarized for each assessment time by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean MRI parameter levels across time will be presented. In addition, Trellis plots of MRI parameters across time for each patient will be presented. A spaghetti plot of grey matter volume against chronological age will also be presented.

10.5.3 Subset Analyses

Exploratory tabular and graphical analyses as described above for efficacy endpoints will be performed both by treatment group and whether or not the patient received treatment or no-treatment in Study HGT-SAN-093 (4 groups).

10.5.4 Exploratory Analyses

[redacted]

10.5.5 Analysis of Health Status

Health status will be assessed by the ITQoL. The observed value and change from baseline in ITQOL Scale Scores will be summarized descriptively for each assessment time by treatment group (Q2W and Q4W groups). Graphical plots of mean scores across time will be presented.

10.5.6 Analysis Health Economics and Outcomes Research

Descriptive statistics, including N, mean, median, and range (for continuous variables), and N and proportions (for categorical variables), for key HCUQ variables, including the number of

emergency room visits, caregiver employment status (FT, PT, and NW), and the number of hours of additional paid help needed by caregivers, over the course of the study. A detailed description of analyses may be provided in a separate pharmacoeconomic analysis plan.

10.6 Analysis of Pharmacokinetic and Pharmacodynamic Data

10.6.1 Pharmacokinetic Measurement and Parameters

The PK population will be used to perform the analysis of the PK data. HGT-1410 concentrations in all collected serum samples will be measured and reported. Individual patient HGT-1410 serum concentration-time profiles will be presented. Individual PK parameters will be derived by a noncompartmental analysis and reported. The actual PK blood sample collection times will be used to determine the individual patient HGT-1410 serum concentration-time profiles. Pharmacokinetic parameters will be calculated if sufficient HGT-1410 concentration-time points exist to derive values. Individual patient CSF HGT-1410 concentrations at each collection time point will be reported.

Pharmacokinetic parameters calculated will include:

- Maximum observed serum concentration (C_{max})
- Time of C_{max} (T_{max})
- Area under the serum concentration-time curve from time zero to the last sampling time at which serum concentrations were measurable ($AUC_{0\text{-last}}$)
- Area under the serum concentration-time curve extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Apparent terminal rate constant (λ_Z) derived from the slope of the log-linear regression of the log-linear terminal portion of the serum concentration-time curve.
- Terminal half-life ($t_{½}$) calculated as $0.693/ \lambda_Z$
- Clearance for IT-L administration ($CL/_F$)
- Volume of distribution based on the terminal phase for IT-L administration (Vz/F)

10.6.2 Pharmacodynamic Analyses

The levels of GAG in CSF and urine are PD endpoints. Analyses of PD endpoints will be performed in the Safety population.

The observed values and changes from baseline in CSF GAG levels will be summarized for each assessment time by treatment group (Q2W and Q4W group). Graphical plot(s) of mean CSF GAG levels across time will be presented. Additionally, Trellis plots of CSF GAG levels across time for each patient will be presented. Furthermore, CSF parameters will be plotted across time for each patient such that the values before and after the first instance of antibody positive status will be indicated using different colors.

The urine GAG levels will be analyzed in a manner similar to that described for CSF data.

10.7 Analysis of Safety

All analyses of safety data will be descriptive and based on the Safety population.

10.7.1 Adverse Events

Once the patient has signed the informed consent form, AEs will be recorded throughout the study and at early termination. AEs will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary.

Treatment-emergent AEs, defined as all AEs from the time of initial IDDD implantation (or first dose if no IDDD implant), to the safety follow-up visit, defined as the last patient visit in the study, will be summarized. For each treatment group, the number and percentage of patients having an AE and the number of events, by system organ class (SOC) and preferred term will be presented. Treatment-emergent AEs will also be summarized by severity and degree of relationship to study drug. In the case of multiple occurrences of the same AE (at the preferred term level) in an individual patient, the AE that is classified as the most severe (ie, maximum severity) will be identified for the analysis by severity and the AE that has the closest relationship to study drug/procedure will be identified for the analysis by relationship. In general, an AE will be considered a treatment-emergent AE if it cannot be definitively categorized otherwise by documentation that its onset preceded either IDDD surgery or first dose.

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

10.7.1.1 Investigational Product

Treatment-emergent AEs deemed by the investigator to be related to HGT-1410 will be summarized by presenting the number and percentage of patients having an AE and the number of events, by SOC and preferred term.

10.7.1.2 IDDD and Surgical Procedure-Related AEs

Intrathecal drug delivery devices and procedure-related AEs will be summarized within MedDRA SOC by preferred term. Separate tabulations will be provided for AEs related to the IDDD, device surgical procedure, and IT administration process.

Intrathecal drug delivery device and procedure related events will be analyzed in the subset of patients in the Safety Population who underwent surgery for IDDD implantation.

10.7.2 Clinical Laboratory Evaluation

The measurements of each laboratory parameter (serum chemistry, hematology, urinalysis and CSF) and the corresponding normal ranges will be converted to Standard International (SI) units, if needed.

Observed values and changes from baseline for continuous laboratory test results will be summarized for each assessment time from baseline. Each laboratory result will be categorized as a patient having had (1) an Abnormal and Clinically Significant (CS) value at any time post-baseline, (2) no CS values at any time post-baseline, but had at least one Abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time post-baseline; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any

time post-baseline that was not CS at baseline (or the most recent non-missing value prior to the start of the treatment), their entire profile for that particular laboratory parameter will be presented as a listing.

If more than one laboratory result is reported per assessment time per parameter, the last non-missing result will be selected for analysis.

10.7.3 ECG Evaluations

The observed values and changes from baseline for continuous variables will be summarized for each assessment time by treatment group. Categorical variables, ie, sinus rhythm and atrial/ventricular hypertrophy, will be summarized in terms of number and percentage of patients in each response category for each assessment time from baseline.

10.7.4 Vital Signs

The observed values and changes from baseline for IT-administration vital signs parameters will be summarized by treatment group. The IT-administration vital signs will also be presented in a trellis plot so that the vital signs data for each IT-administration within a patient will be presented on a single page.

10.7.5 Anti-rhHNS antibody in Serum and CSF

Serum and CSF anti-rhHNS antibody status (ie, positive or negative) at each assessment time from baseline will be summarized in terms of counts and proportion for the treatment groups. Additionally, semi-logarithmic plot of serum and CSF anti-rhHNS antibody titers across the study visits in the patients exhibiting seropositivity will also be presented.

10.7.6 Concomitant Medications

Concomitant medications will be coded using the WHO-DD. The concomitant medications that occur from the time of the surgery for IDDD implantation to the safety follow-up visit, defined as the last patient visit in the study, will be summarized by therapeutic class and preferred term.

10.7.7 Other Observations Related to Safety

10.7.7.1 IDDD Performance

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

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

The proportion of patients for whom a successful first injection of study drug occurred will be reported among those for whom a first injection was attempted (i.e. those who had an apparently successful implantation and did not suffer a device removal or revision prior to first scheduled injection). The proportion of patients who had no failed injection attempts during the study will also be summarized. The corresponding 95% confidence intervals of the proportion of interest will be estimated, where appropriate. Injections that are not administered for patient-related reasons (e.g. patient uncooperative, competing medical issue, etc) will not be included in the determination of the success of injection rate.

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

No statistical modeling or covariate adjustment is planned due to the small sample size.

10.8.2 Handling of Dropouts or Missing Data

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

10.8.3 Interim Analyses and Data Monitoring

No formal interim analysis or interim statistical testing for early stopping of the trial is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting or general planning purposes. An independent DMC will be established to provide an ongoing, independent review and assessment of patient data, and to safeguard the interests and safety of the participating patients in the study (see Section 11.8). An analysis of the data for DMC review will occur at specific times during the study as specified in the DMC charter. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.

10.8.4 Multicenter Studies

Data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. In order to maintain desirable level of inter-rater reliability for BSID-III/KABS-II and VABS-II assessments/interviews, standardized training of the raters and parents will be conducted. Furthermore, a central reader will evaluate all MRI data.

10.8.5 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed.

10.8.6 Sensitivity Analyses

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

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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.

The protocol and any applicable documentation will be submitted or notified to the relevant Regulatory Authorities in accordance with the regulations of the countries involved in the trial.

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

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

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the 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).

After reading the informed consent document, the patient or 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, 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 or 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 of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorized representative. 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 or 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 patient initials will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. 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 eCRF's for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

11.7 Case Report Forms and Study Records

11.7.1 Case Report Forms

Case report forms (paper or electronic) are provided for each 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 resigning the eCRF.

11.7.2 Critical Documents

Before Shire initiates the trial (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 12 months of study initiation)
- Copy of Investigator and sub-investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Patient Information/Informed Consent Form, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/IEC Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

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

11.8 Data Monitoring Committee

An independent DMC will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The DMC will consist of a biostatistician and 2 clinical experts.

It is anticipated that there will be scheduled meetings annually during the conduct of the study. The first meeting will be an orientation meeting and will take place prior to the start of the study. Subsequent meetings will occur at specific times during the study as specified in the DMC charter. The final meeting will be conducted when all patients have completed the study for a comprehensive safety overview of the study. A special DMC meeting will be convened if the safety-related study stopping rules are met (refer to Section 7.16).

The DMC will adhere to a prospectively determined charter, which will be written by Shire and approved by the DMC. The charter will define the responsibilities of the DMC and Shire, describe the conduct of the meetings and define the data sets to be reviewed. The DMC will also be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter.

The DMC will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC 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 will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to

discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

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

11.11 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable 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 product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the 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 (or its designee) may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.13 Data Generation and Analysis

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

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

11.14 Retention of Data

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

11.15 Financial Disclosure

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

11.16 Publication and Disclosure Policy

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

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

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

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Appendix 1 Study Schedule of Events for Group 1: Maintaining HGT-1410 Q2W

	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				Follow-up
	Weeks[a]																				
Procedure	50	52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	122, 124, 126, 128, 130	132	134, 136, 138, 140, 142	144	146, 148, 150, 152, 154	156	158, 160, 162, 164, 166	168	172[h]
Informed consent	•																					
Review of inclusion/exclusion criteria	•																					
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Full PE including Height, Weight, and Head Circumference					•				•				•				•				•	
Symptom-directed PE	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/KABC-II[c]					•				•				•				•				•	
VABS-II					•				•				•				•				•	
ITQoL[d]					•				•				•				•				•	
HCUQ					•				•				•				•				•	
ECG[e]									•								•				•	
Hematology			•		•		•		•		•		•		•		•		•		•	•
Serum chemistry			•		•		•		•		•		•		•		•		•		•	•
Urinalysis			•		•		•		•		•		•		•		•		•		•	•
MRI of the head									•								•					
MRI of liver and spleen									•								•					
HGT-1410 administration	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing			•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•	

Procedure	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				Follow-up
	Weeks[a]																				
	50	52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	122, 124, 126, 128, 130	132	134, 136, 138, 140, 142	144	146, 148, 150, 152, 154	156	158, 160, 162, 164, 166	168	172[h]
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[g]									•													
CSF sample for storage for biomarkers	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, & procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab = antibody; AE = adverse event; BSID-III = Bayley Scales of Infant and Toddler Development III; CSF = cerebrospinal fluid; con meds = concomitant medications; ECG = electrocardiogram; HCUQ = Healthcare Utilization Questionnaire; HNS = heparan N-sulfatase; ITQoL = Infant Toddler Quality of Life questionnaire; KABC-II = Kaufman Assessment Battery for Children-Second Edition; MRI = Magnetic resonance imaging; PE = physical examination; PK = pharmacokinetics; PT and aPTT = prothrombin time and activated partial thromboplastin time; rhHNS = recombinant human heparan N-sulfatase; VABS II = Vineland Adaptive Behavior Scale

[a] Time point for weeks refers to the start of the week.

[b] Vital signs during the treatment period will be obtained immediately prior to IT dosing.

[c] KABC-II will be used if and when a child ages out of the BSID and his/her cognitive status permits the use of the KABC-II.

[d] For patients ≤ 5 years of age

[e] ECGs are to be performed after study drug administration.

[f] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[g] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[h] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 172.

Appendix 2 Study Schedule of Events for Group 2: Maintaining HGT-1410 Q4W

Procedure	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																				Follow-up
	Weeks[a]																				
	52	56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124, 128	132	136, 140	144	148, 152	156	160, 164	168	172[h]
Informed consent	•																					
Review of inclusion/exclusion criteria	•																					
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Full PE including Height, Weight, and Head Circumference					•				•				•				•				•	
Symptom-directed PE	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/ KABC-II[c]					•				•				•				•				•	
VABS-II					•				•				•				•				•	
ITQoL[d]					•				•				•				•				•	
HCUQ					•				•				•				•				•	
ECG[e]									•								•				•	
Hematology			•		•		•		•		•		•		•		•		•		•	•
Serum chemistry			•		•		•		•		•		•		•		•		•		•	•
Urinalysis			•		•		•		•		•		•		•		•		•		•	•
MRI of the head									•								•					
MRI of liver and spleen									•								•					
HGT-1410 administration	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing			•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing			•		•		•		•		•		•		•		•		•		•	

Procedure	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																				Follow-up
	Weeks[a]																				
	52	56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124, 128	132	136, 140	144	148, 152	156	160, 164	168	172[h]
(serum and CSF) and CSF biomarker testing																						
Serum PK sampling[g]									•													
CSF sample collection for storage for biomarkers	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, & procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse event monitoring	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab = antibody; AE = adverse event; BSID-III = Bayley Scales of Infant and Toddler Development III; CSF = cerebrospinal fluid; con meds = concomitant medications; ECG = electrocardiogram; HCUQ = Healthcare Utilization Questionnaire; HNS = heparan N-sulfatase; ITQoL = Infant Toddler Quality of Life questionnaire; KABC-II = Kaufman Assessment Battery for Children-Second Edition; MRI = Magnetic resonance imaging; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PT and aPTT = prothrombin time and activated partial thromboplastin time; rhHNS = recombinant human heparan N-sulfatase; VABS II = Vineland Adaptive Behavior Scale

[a] Time point for weeks refers to the start of the week.

[b] Vital signs during the treatment period will be obtained immediately prior to IT dosing.

[c] KABC-II will be used if and when a child ages out of the BSID and his/her cognitive status permits the use of the KABC-II.

[d] for patients ≤ 5 years of age

[e] ECGs are to be performed after study drug administration

[f] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410

[g] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[h] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 172.

Appendix 3 Study Schedule of Events for Group 3A: Initiating HGT-1410 Q2W

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																					Follow-up
Procedure	Days		Weeks[a]																																						
	-21 to -7	Post op check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]
Informed consent	•																																							
Review of inclusion/exclusion criteria	•																																							
Randomization	•																																							
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigator assessment of vision and hearing ability	•																																							
Full PE including Height, Weight, and Head Circumference	•[c]														•												•				•				•				•		
Symptom-directed PE		•	•	•	•	•	•	•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/KABC-II[d]	•[e]														•												•				•				•				•		
VABS-II	•[e]														•												•				•				•				•		
ITQoL[f]	•[e]														•												•				•				•				•		
HCUQ	•[e]														•												•				•				•				•		
ECG[g]	•		•		•		•		•		•		•		•												•								•				•		
Hematology	•		•		•		•		•		•		•		•						•						•		•		•		•		•		•		•		•

Procedure	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
	Days		Weeks[a]																																						
	-21 to -7	Post op check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]
PT and aPTT	•																																							
Serum chemistry	•		•		•		•		•		•		•		•						•						•		•		•		•		•		•		•	•
Urinalysis	•		•		•		•		•		•		•		•						•						•		•		•		•		•		•		•	•
MRI of the head	•[h]														•												•								•					
MRI of liver and spleen	•[h]														•												•								•					
IDDD implantation	•																																						
X-Ray to check IDDD placement	•																										•												
Post-operative check of IDDD incision		•[i]																										•											
HGT-1410 administration			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing	•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•						•						•						•		•		•		•		•		•		•	
Serum PK sampling[k]			•																								•								•					

Procedure	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
	Days		Weeks[a]																																				
	-21 to -7	Post op check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]
CSF PK sampling[k]			•																							•													
CSF sample for storage for biomarkers	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, & procedures	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab = antibody; AE = adverse event; BSID-III = Bayley Scales of Infant and Toddler Development III; CSF = cerebrospinal fluid; con meds = concomitant medications; ECG = electrocardiogram; HCUQ = Healthcare Utilization Questionnaire; HNS = heparan N-sulfatase; ITQoL = Infant Toddler Quality of Life questionnaire; KABC-II = Kaufman Assessment Battery for Children-Second Edition; MRI = Magnetic resonance imaging; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PT and aPTT = prothrombin time and activated partial thromboplastin time; rhHNS = recombinant human heparan N-sulfatase; VABS II = Vineland Adaptive Behavior Scale

[a] Time point for weeks refers to the start of the week.

[b] Vital signs at Weeks 0-48 will be obtained immediately prior to IT dosing, and at 15, 30, 45, 60, 90, and 120 minutes, and 2.5, 3, and 4 hours after dosing. Vital signs at Weeks 50-120 will be obtained immediately prior to IT dosing.

[c] Head circumference will only be measured at screening.

[d] KABC-II will be used if and when a child ages out of the BSID and his/her cognitive status permits the use of the KABC-II.

[e] Cognitive assessments are to be performed before IDDD implantation. The Week 48 assessments from Study HGT-SAN-093 will be used as the baseline assessments in Study SHP-610-201. If the Week 48 assessments from Study HGT-SAN-093 are missing, these assessments will need to be performed prior to IDDD implantation in the extension study.

[f] for patients ≤ 5 years of age

[g] ECGs are to be performed after study drug administration

[h] If scheduling does not permit the MRI assessments to be performed during IDDD implantation (under the same general anesthetic), then these procedures should be done before the first dose of HGT-1410 at D-1. This would require administration of anesthesia.

	IDDD Implant-ation Period	Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
Procedure	Days	Weeks[a]																																				
	-21 to -7	Post op check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]

[i] Post-operative check of IDDD incision (1 to 3 days after operation) along with con med, therapies, and procedures and AE monitoring.

[j] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410

[k] Serum and CSF PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[l] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 124.

Appendix 4 Study Schedule of Events for Group 3B: Initiating HGT-1410 Q4W

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	Days		Weeks[a]																				
	-21 to -7	Post op check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[k]
Informed consent	•																						
Review of inclusion/exclusion criteria	•																						
Randomization	•																						
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigator assessment of vision and hearing ability	•																						
Full PE including Height, Weight, and Head Circumference	•[c]						•				•				•				•				
Symptom-directed PE		•	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•	•
BSID-III/ KABC-II[d]	•[e]						•				•				•				•				•
VABS-II	•[e]						•				•				•				•				•
ITQoL[f]	•[e]						•				•				•				•				•
HCUQ	•[e]						•				•				•				•				•
ECG[g]	•		•	•	•	•	•				•								•				•
Hematology	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
PT and aPTT	•																						
Serum chemistry	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
Urinalysis	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
MRI of the head	•[h]						•				•								•					

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	Days		Weeks[a]																				
	-21 to -7	Post op check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[d]
MRI of liver and spleen	•[h]						•				•								•					
IDDD implantation	•																							
X-Ray to check IDDD placement	•																							
Post-operative check of IDDD incision		•[i]																						
HGT-1410 administration			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing	•		•	•	•	•	•	•	•	•	•		•		•		•		•		•		•	
Urine sample for GAG			•	•	•	•	•	•	•	•	•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•	•	•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[k]			•								•								•					
CSF PK sampling[k]			•								•													
CSF sample collection for storage for biomarkers	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, & procedures	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse event monitoring	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab = antibody;AE = adverse event; BSID-III = Bayley Scales of Infant and Toddler Development III; CSF = cerebrospinal fluid; con meds = concomitant medications; ECG = electrocardiogram; HCUQ = Healthcare Utilization Questionnaire; HNS = heparan N-sulfatase; ITQoL = Infant Toddler Quality of Life questionnaire; KABC-II = Kaufman Assessment Battery for Children-Second Edition; MRI = Magnetic resonance imaging; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PT and aPTT = prothrombin time and activated partial thromboplastin time; rhHNS = recombinant human heparan N-sulfatase; VABS II = Vineland

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	Days		Weeks[a]																				
	-21 to -7	Post op check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[l]

Adaptive Behavior Scale

[a] Time point for weeks refers to the start of the week.

[b] Vital signs at Weeks 0-48 will be obtained immediately prior to IT dosing, and at 15, 30, 45, 60, 90, and 120 minutes, and 2.5, 3, and 4 hours after dosing. Vital signs at Weeks 50-120 will be obtained immediately prior to IT dosing.

[c] Head circumference will only be measured at screening.

[d] KABC-II will be used if and when a child ages out of the BSID and his/her cognitive status permits the use of the KABC-II.

[e] Cognitive assessments are to be performed before IDDD implantation. The Week 48 assessments from Study HGT-SAN-093 will be used as the baseline assessments in Study SHP-610-201. If the Week 48 assessments from Study HGT-SAN-093 are missing, these assessments will need to be performed prior to IDDD implantation in the extension study.

[f] for patients ≤ 5 years of age

[g] ECGs are to be performed after study drug administration

[h] If scheduling does not permit the MRI assessments to be performed during IDDD implantation (under the same general anesthetic), then these procedures should be done before the first dose of HGT-1410 at D-1. This would require administration of anesthesia.

[i] Post-operative check of IDDD incision (1 to 3 days after operation) along with con med, therapies, and procedures and AE monitoring.

[j] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[k] Serum and CSF PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[l] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments done at Week 124.

Appendix 5 Pharmacokinetic and Pharmacodynamic Sample Schedule

Drug Administration	PK / PD Sampling Times
	Blood Sampling
HGT-1410 IT injection	Serum PK samples will be obtained at Weeks 0 (Groups 3A and 3B only), 48, and 96. Immediately prior to IT injection (baseline), then at 0.5, 1, 2, 4, 8, 12, 24, and 48 (Day 2) hours following completion of IT injection. Patients may be discharged from the hospital after the 24-hour blood draw. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); in consultation with the Investigator. Patients will return to the hospital for PK blood sampling at the 48-hour PK time point. Patients will be discharged for home following the last (48-hour) PK time point and following the completion of their final physical examination.
	CSF Sampling
	CSF PK and PK/PD samples will be obtained at Weeks 0 and 48 for Groups 3A and 3B only. Immediately prior to IT injection (baseline), then at 4 hours and 48 hours after the completion of the IT injection. The 4 hour and 48 hour post-dose CSF samples will only be obtained if a functioning IDDD is in place. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); in consultation with the Investigator. Patients will return to the hospital for CSF sampling at the 48 hour time points.

Appendix 6 Expected SOPH-A-PORT ® Mini S Adverse Device Effects

Procedure-Related Complications

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

Study Title: A Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy Study of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease

Study Number: SHP-610-201

Final Date: 23 September 2014

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

[redacted] _____ [redacted]
Signature **Date**

[redacted], MD
_____
Printed Name

Clinical Trial Protocol: SHP-610-201

Study Title:	An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease
Study Number:	SHP-610-201
Study Phase:	IIb
Product Name:	HGT-1410
Device Name:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
IND Number:	102165
EUDRACT Number	2014-003960-20
Indication:	Long-term Treatment of Mucopolysaccharidosis Type IIIA (MPS IIIA or Sanfilippo Syndrome Type A)
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc.
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA +1-617-349-0200
Medical Monitor:	[redacted], DO

	Date
Original Protocol:	23 September 2014
Amendment 1:	17 December 2015

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc. (Shire)

Name of Finished Product:

HGT-1410 (Recombinant Human Heparan N Sulfatase, or rhHNS)

Name of Device:

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

Study Title:

An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease

Study Number:

SHP-610-201

Study Phase: IIb

Investigational Product, Dose, and Mode of Administration:
HGT-1410 at a dose of 45 mg administered every 2 weeks (Q2W) or 45 mg administered every 4 weeks (Q4W). HGT-1410 will be administered intrathecally (IT) by an indwelling IT drug delivery device (IDDD).

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-1410 indicated for intrathecal delivery intermittently over a long period of time.

Comparator, Dose, and Mode of Administration:

Not applicable

Primary Objective(s):

To evaluate long-term safety in patients with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo syndrome type A) who received HGT-1410

Secondary Objective(s):

To evaluate:

- The long-term cognitive function as measured by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II), age-equivalent and developmental quotient (DQ) scores in patients with MPS IIIA who received HGT-1410
- The long-term adaptive behavioral function, assessed by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) in patients who received HGT-1410
- The total cortical grey matter volume, as assessed by volumetric magnetic resonance imaging (MRI) of the brain, in patients who received HGT-1410

Exploratory Objective:

[redacted]

Pharmacokinetic and Pharmacodynamic Objectives

To evaluate:

- The pharmacokinetics of HGT-1410 in serum
- The pharmacokinetics of HGT-1410 in cerebrospinal fluid (CSF), in patients who received no treatment in Study HGT-SAN-093
- The concentration of glycosaminoglycans (GAG) in CSF and urine in patients who received HGT-1410

Health Status Objective

To evaluate health status as measured by the Infant Toddler Quality of Life Questionnaire™ (ITQoL) instrument in patients who received HGT-1410

Health Economics and Outcomes Research Objectives

To evaluate healthcare resource utilization, as evaluated by the Healthcare Utilization Questionnaire (HCUQ), in patients who received HGT-1410

Study Endpoints:

Safety evaluations include the assessment of adverse events (AEs), IDDD-related issues, laboratory values, anti-rhHNS antibody development, vital signs, physical examination findings, and electrocardiogram (ECG) results.

The secondary endpoints of this study are:

- The change from Baseline in BSID-III or KABC-II age-equivalent, DQ, and developmental delay scores
- The change from Baseline in adaptive behavioral function domains, assessed by VABS II, using raw scores, age-equivalent scores, and DQ scores
- The change from Baseline in total cortical grey matter volume, as assessed by MRI

[redacted]

The pharmacokinetic endpoint is to determine the pharmacokinetic behavior of HGT-1410 in serum. The pharmacokinetic behavior of HGT-1410 in CSF will also be determined in patients who received no treatment in Study HGT-SAN-093.

The pharmacodynamic endpoint is to determine the GAG concentrations in CSF and urine.

The health status endpoint is the ITQoL scores at each assessment time and the corresponding change from Baseline.

The health economic and outcome research endpoints evaluate key HCUQ variables, such as the number of emergency room visits, caregiver employment status (full-time, part-time, or not working), and the number of hours of additional paid help needed by caregivers over the course of the study.

Study Population:

A maximum of 21 patients with MPS IIIA and who completed Study HGT-SAN-093 are planned to enroll in this study.

Study Design:

This is an open-label study for patients who completed through at least the Week 48 Visit of Study HGT-SAN-093. Patients who originally received HGT-1410 in Study HGT-SAN-093 will remain on the same dosing regimen as they received in Study HGT-SAN-093; Group 1 will receive HGT-1410 Q2W and Group 2 will received HGT-1410 Q4W. Patients in Groups 1 and 2 will begin treatment at Week 50 and Week 52, respectively, of this extension study (Study SHP-610-201). Patients who originally received no treatment in Study HGT-SAN-093 (Group 3) will receive an IDDD following informed consent and will be re-randomized in a 1:1 allocation ratio to receive HGT-1410 via a Q2W or Q4W dosing regimen (Groups 3A and 3B, respectively) in Study SHP-610-201. Patients in Groups 3A and 3B will begin treatment on Week 0 of the extension study.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all IT injections of HGT-1410. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual(s), which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug may be administered and CSF sampled by lumbar puncture (LP). General anesthesia or sedation may be required for injections of study drug and some evaluations and can be used at the discretion of the Investigator. 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, extension study, expanded access program, commercially available, etc.).

Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of Study SHP-610-201. For patients who received HGT-1410 in Study HGT-SAN-093, a serum pharmacokinetic sample will be obtained at the Week 96 visit (after approximately 2 full years of exposure to HGT-1410 across Study HGT-SAN-093 and SHP-610-201). For patients who received no treatment in Study HGT-SAN-093, serum pharmacokinetic samples will be obtained at the Week 0, 48, and 96 visits, and CSF pharmacokinetic samples will be obtained at the Week 0 and 48 visits in Study SHP-610-201.

Study Duration:

Approximately 30 months of treatment with HGT-1410 will occur during the study.

Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no-treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

1. Patient has completed through at least the Week 48 visit of Study HGT-SAN-093.
2. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/ethics committee–approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

Exclusion Criteria:

Patients will be excluded from the study if any of the following criteria are met:

1. The patient, if randomized to treatment in Study HGT-SAN-093, has experienced a decline of more than 20 points in the BSID-III cognitive DQ score between Baseline and the Week 48 visit in Study HGT-SAN-093, AND, upon individual evaluation by the Investigator, has been deemed a treatment failure*.
2. The patient has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with HGT-1410, including but not limited to clinically relevant intracranial hypertension, severe infusion-related reactions after treatment with HGT-1410, or uncontrollable seizure disorder.
3. The patient has a known hypersensitivity to any of the components of HGT-1410. Patients with documented infusion-related reactions that are clinically manageable (for example, with pre-medication or slowing infusion rate) are not necessarily excluded based on the assessment of the investigator.
4. The patient is enrolled in another clinical study, other than HGT-SAN-093, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
    a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device.
    b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator.
    c. The patient's drug therapy requires substances known to be incompatible with the materials of construction.
    d. The patient has a known or suspected local or general infection.
    e. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
    f. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation.

g. The patient has a functioning CSF shunt device.
h. The patient has shown an intolerance to an implanted device.

7. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations or is otherwise unlikely to complete the study) as determined by the Investigator.

*All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in the BSID-III DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

Efficacy Assessments:

Efficacy variables to be assessed will include cognitive function expressed as a DQ assessed by neurocognitive testing using the BSID-III/KABS-II; adaptive behavioral function over time, assessed by VABS-II; the total cortical grey matter volume and liver and spleen size as assessed by MRI; quality-of-life score (assessed using the ITQoL); and health care resource utilization (assessed using the HCUQ).

Pharmacokinetic Assessments:

The determination of HGT-1410 concentration in serum for all patients and in CSF for patients who received no treatment in Study HGT-SAN-093.

Pharmacodynamic Assessments:

The determination of GAG concentrations in CSF and urine

Safety Assessments:

Safety will be assessed during the study by the following:

- Collection of AEs (by type, severity, and relationship to treatment [HGT-1410, the IDDD, device surgical procedure, or IT administration process])
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Physical examination
- Vital signs
- Twelve-lead ECG recordings
- CSF laboratory parameters (chemistries, cell counts)
- Anti-rhHNS antibodies in CSF and serum, including determination of antibodies having enzyme neutralizing activity

Statistical Methods:

The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial. Any hypothesis tests will be 2-sided and will be viewed as exploratory. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. Summary statistics for continuous variables will

include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time, as appropriate.

Unless otherwise indicated, all summary statistics will be presented by treatment group (either Q2W or Q4W) to which the patients were randomly assigned (patients who were initially assigned to Q2W or Q4W group in Study HGT-SAN-093 or patients who received no-treatment in Study HGT-SAN-093 and were randomly assigned to Q2W or Q4W in Study SHP-610-201). Additional analyses in the subgroup of patients who received no-treatment in Study HGT-SAN-093 may be performed.

All safety data will be summarized descriptively. The change from baseline at each time point for efficacy outcomes will be summarized. Generally, the mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented. Additional efficacy analyses in the subgroups of patients previously treated and untreated in Study HGT-SAN-093 may be performed.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis. The data included for treated patients in HGT-SAN-093 starts from the baseline of Study HGT-SAN-093 and for patients who received no treatment in HGT-SAN-093 from the baseline of Study SHP-610-201. Baseline is the assessment obtained during the initial study period, prior to the first dose of HGT-1410, regardless of whether this occurred in Study HGT-SAN-093 or SHP-610-201.

Date of Original Protocol: 23 September 2014

Date of Amendment 1: 17 December 2015

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT; SGPT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST; SGOT	aspartate aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{0\text{-last}}$	area under the curve from the time of dosing to the last measurable concentration
$AUC_{0\text{-}\infty}$	area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
BBB	blood-brain barrier
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CK	creatine kinase
$CL/_F$	total body clearance for extravascular administration divided by the fraction of dose absorbed
Cl	chloride
C_{max}	maximum concentration occurring at t_{max}
CNS	central nervous system
CO_2	carbon dioxide
con meds	concomitant medications
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
DMC	Data Monitoring Committee
DQ	developmental quotient
DS	dermatan sulfate
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FT	full-time

Abbreviation	Definition
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hct	hematocrit
HCUQ	Healthcare Utilization Questionnaire
Hgb	hemoglobin
HNS	heparan N-sulfatase
HS	heparan sulfate
ICH	International Conference on Harmonisation
IDDD	intrathecal drug delivery device
IFU	Instructions for Use
IRB	Institutional Review Board
IT	Intrathecal(ly)
ITQoL	Infant Toddler Quality of Life Questionnaire™
ITT	intent-to-treat
IV	intravenous(ly)
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactate dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPS IIIA	mucopolysaccharidosis type IIIA or Sanfilippo syndrome type A
MRI	magnetic resonance imaging
NA	sodium
NCS	not clinically significant
NW	not working
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetics
PT	part-time
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
RBC	red blood cell
rhHNS	recombinant human heparan N sulfatase

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SGSH	sulfoglucosamine sulfohydrolase
SI	Standard International
SOC	system organ class
$t_{1/2}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
UADE	unanticipated adverse device effect
US(A)	United States (of America)
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
$V_{z/F}$	volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WBC	white blood cell
WHO-DD	World Health Organization-Drug Dictionary
λ_Z	first order rate constant associated with the terminal (log-linear) portion of the curve

1 INTRODUCTION

Mucopolysaccharidosis type IIIA (MPS IIIA, also called Sanfilippo syndrome type A) is a rare, autosomal recessive, lysosomal storage disease (LSD) presenting in early childhood that causes progressive neurodegeneration associated with intractable behavioral problems and developmental regression. Ultimately, a vegetative state supervenes. Life span is shortened, with death usually occurring in the late teen years. The genetic defect in this disorder is a mutation in both copies of the sulfoglucosamine sulfohydrolase (SGSH) gene, located on chromosome 17, which encodes the lysosomal enzyme, sulfoglucosamine sulfohydrolase, also called heparan-N-sulfatase, or sulfamidase. This enzyme is necessary for the normal intralysosomal catabolism of the glycosaminoglycan (GAG) (formerly termed mucopolysaccharide), heparan sulfate (HS). Sulfoglucosamine sulfohydrolase deficiency therefore results in the accumulation of heparan sulfate in lysosomes. Although the metabolic defect is expressed in every organ, the clinical manifestations of disease are primarily neurological. These are not usually apparent until 1 to 4 years of age. The molecular events linking the primary metabolic defect to the consequent neuropathology are not understood.

MPS III is the most prevalent of the mucopolysaccharidoses and consists of 4 subtypes, A, B, C, and D.[1] Each of these is characterized by a deficiency of a distinct lysosomal enzyme necessary for the degradation of heparan sulfate. Clinically, on an individual patient level, the 4 subtypes cannot be reliably distinguished. Globally, subtype A is the most prevalent, at approximately 1 case in 100,000 live births, followed by subtype B, at approximately 1 in 250,000 live births.[1-3] Among MPS IIIA patients, there is wide allelic heterogeneity, with at least 100 SGSH mutations described to date. Most of these are missense, but nonsense mutations, deletions, insertions and splice-site mutations also occur.[4]

MPS IIIA symptoms usually arise in the first or second year of life, although diagnosis is delayed until an average age of 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors that include aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5-7] There are also reports of unexplained, recurrent and severe diarrhea.[6] Overall, individuals with MPS IIIA exhibit progressive dementia with ultimate inanition and death resulting from the CNS disease. Lifespan is severely curtailed, with usual survival into the late teens.[6] Milder variants are recognized, with slower progression and survival to later age. The latter has been reported in approximately 10% of German patients with MPS IIIA, in association with the presence of the S298P mutation.[8]

No effective, disease-modifying therapies are currently approved as treatments for this devastating and disabling disease. A goal of Shire is to develop recombinant human heparan-N-sulfatase (rhHNS, development name HGT-1410) as enzyme replacement therapy (ERT) for patients with MPS IIIA. A particular problem for lysosomal storage disorders that damage the brain, such as MPS III, is how to target ERT to the brain, as macromolecules cannot cross the blood-brain barrier (BBB).[9] In animal studies, ERT has been administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV) it does not cross the BBB after the immediate postnatal period of life. HGT-1410 has been

shown to be ineffective if administered intravenously in the MPS IIIA mouse model, in contrast to its efficacy in treating CNS pathology when administered into the CSF.[10]

In order to traverse the BBB, HGT-1410 will be administered directly to the CNS using an IT drug delivery device (IDDD) or, if the IDDD is non-functional, via lumbar puncture (LP). The advantage of using an IDDD is the potential to obviate the need for multiple LPs for drug delivery. HGT-1410 will be administered through the IDDD or, if the IDDD is non-functional, via LP.

Please refer to the current edition of the Investigator's Brochure for further information concerning the nonclinical studies completed, including safety and clinical development of HGT-1410.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate long-term safety in patients with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo syndrome type A) who received HGT-1410.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- The long-term cognitive function as measured by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II), age-equivalent and developmental quotient (DQ) scores in patients with MPS IIIA who received HGT-1410
- The long-term adaptive behavioral function, assessed by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) in patients who received HGT-1410
- The total cortical grey matter volume, as assessed by volumetric magnetic resonance imaging (MRI) of the brain, in patients who received HGT-1410

2.3 Exploratory Objective

The exploratory objective of this study is [redacted].

2.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic and pharmacodynamics objectives of this study are to evaluate:

- The pharmacokinetics of HGT-1410 in serum
- The pharmacokinetics of HGT-1410 in CSF, in patients who received no treatment in Study HGT-SAN-093
- The concentration of GAG in CSF and urine in patients who received HGT-1410

2.5 Health Status Objective

The health status objective of this study is to evaluate health status as measured by the Infant Toddler Quality of Life Questionnaire™ (ITQoL) instrument in patients who received HGT-1410.

2.6 Health Economics and Outcome Research Objective

The health economics and outcome research objective of this study is to evaluate healthcare resource utilization, as evaluated by the Healthcare Utilization Questionnaire (HCUQ), in patients who received HGT-1410.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

Safety is the primary objective of the study and will be assessed during the study by the following:

- Collection of adverse events (AEs; by type, severity, and relationship to treatment [HGT-1410, the IDDD, device surgical procedure, or IT administration process])
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Physical examination
- Vital signs
- Twelve-lead electrocardiogram (ECG) recordings
- CSF laboratory parameters (including chemistries, cell counts)
- Anti-rhHNS antibodies in CSF and serum, including determination of antibodies having enzyme neutralizing activity

3.2 Secondary Endpoints

The secondary endpoints of this study are:

- The change from Baseline in BSID-III or KABC-II age-equivalent, DQ, and developmental delay scores
- The change from Baseline in adaptive behavioral function domains, assessed by VABS II, using raw scores, age-equivalent scores, and DQ scores
- The change from Baseline in total cortical grey matter volume, as assessed by MRI

3.3 Exploratory Endpoint(s)

[redacted]

3.4 Pharmacokinetic and Pharmacodynamic Endpoints

The pharmacokinetic endpoint is to determine the pharmacokinetic behavior of HGT-1410 in serum, based on the following parameters:

- Maximum concentration occurring at t_{max} (C_{max})
- Time of maximum observed concentration sampled during a dosing interval (t_{max})
- Area under the curve from the time of dosing to the last measurable concentration ($AUC_{0\text{-}last}$)
- Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration ($AUC_{0\text{-}\infty}$)
- First order rate constant associated with the terminal (log-linear) portion of the curve (λ_Z)
- Terminal half-life ($t_{1/2}$) calculated as $0.693/\lambda_Z$

- total body clearance for extravascular administration divided by the fraction of dose absorbed ($CL/_F$)
- Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed ($V_z/_F$)

The pharmacodynamic endpoint is to determine the GAG concentrations in CSF and urine.

3.5 Health Status Endpoint

The health status endpoint is the ITQoL scores at each assessment time and the corresponding change from Baseline.

3.6 Health Economics and Outcomes Research Endpoint

The health economic and outcome research endpoints evaluate the key HCUQ variables, such as the number of emergency room visits, caregiver employment status (full-time [FT], part-time [PT], and not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label extension study of HGT-1410 for patients who completed through at least the Week 48 Visit in Study HGT-SAN-093. The study design is presented in Figure 1. Patients who originally received HGT-1410 in Study HGT-SAN-093 will remain on the same dosing regimen as they received in Study HGT-SAN-093; Group 1 will receive HGT-1410 Q2W and Group 2 will received HGT-1410 Q4W. Patients in Groups 1 and 2 will begin treatment at Week 50 and Week 52, respectively, of this extension study (Study SHP-610-201). Patients who originally received no-treatment in Study HGT-SAN-093 (Group 3) will receive an IDDD following informed consent and will be re-randomized in a 1:1 allocation ratio to receive HGT-1410 via a Q2W or Q4W dosing regimen (Groups 3A and 3B, respectively) in Study SHP-610-201. Patients in Groups 3A and 3B will begin treatment on Week 0 of the extension study.

The Sponsor and Principal Investigator will consider the feasibility of transitioning the patient's IT dosing to local sites to reduce the burden imposed by travel. The local sites will be selected and approved by the Sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: The main site may serve as a local site as needed, and in this case, the main site will follow the assessment schedule for a local site). The qualification requirements for physicians at local sites will be identical to those for the main sites. Local sites will be experienced with IT administration via an IDDD. For patients who were in the no-treatment group in the HGT-SAN-093 study, initial IT administrations will be at the main study site following IDDD implantation until in the opinion of the Principal Investigator there are no safety or medical concerns precluding the patient from transitioning. Patients will be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the Investigator. Exceptions include the IT injections of HGT-1410 when scheduled study assessments are scheduled; these will take place at the main site. Patients that have already received IT drug administration at the main study site would be eligible to transfer to a local site starting at Week 50 (Group 1) or Week 52 (Group 2) in SHP-610-201 if in the opinion of the Principal Investigator there are no safety or medical concerns precluding the patient from transitioning.

It is anticipated that the IDDD will be used to collect CSF samples and to deliver IT injections of HGT-1410 and preservative-free saline flushes. No other medication will be administered through the device. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual, which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug 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. General anesthesia or sedation may be required for injections of study drug and some evaluations, and may be used at the discretion of the Investigator. The Data Monitoring Committee (DMC) will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter (see Section 11.8).

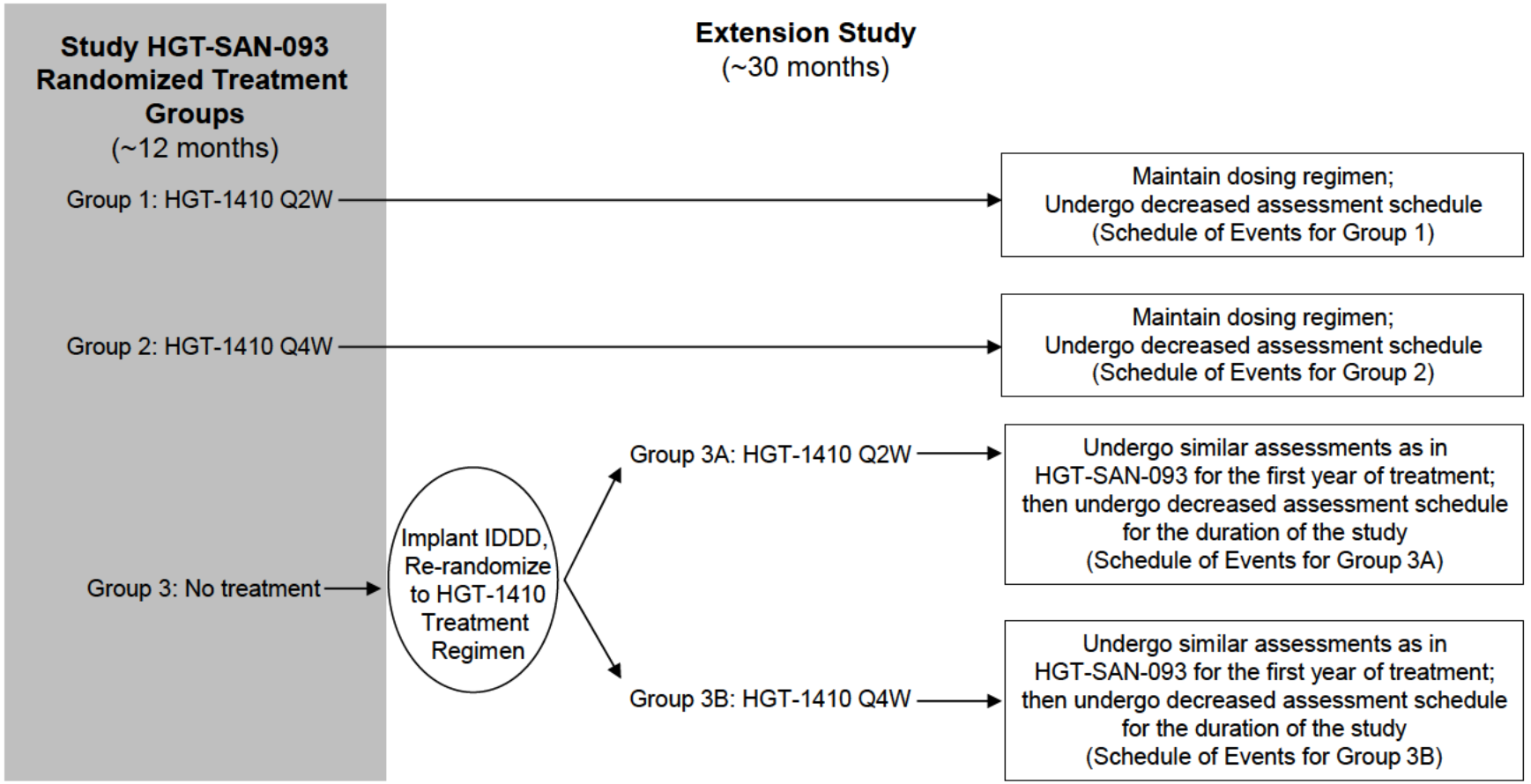
Patients will have the IDDD removed when they discontinue from or complete the study unless the patient is continuing to receive product or treatment through another mechanism (eg, extension study, expanded access program, commercially available drug).

Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of the extension study. A pharmacokinetic sample for patients who received HGT-1410 in Study HGT-SAN-093 will be obtained at the Week 96 visit (after approximately 2 full years of exposure to HGT-1410 across Studies HGT-SAN-093 and SHP-610-201). Serum pharmacokinetic samples for patients who received no-treatment in Study HGT-SAN-093 will be obtained at the Week 0, 48, and 96, and CSF pharmacokinetic samples will be obtained on the Week 0 and 48 visits in Study SHP-610-201.

Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

See Appendix 1, Appendix 2, Appendix 3, and Appendix 4 for the Study Schedule of Events tables for Groups 1, 2, 3A, and 3B, respectively.

Figure 1 SHP-610-201 Study Design



Abbreviations: IDDD=intrathecal drug delivery device; Q2W=every 2 weeks; Q4W=every 4 weeks

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

The study design is intended to provide ongoing treatment with HGT-1410 to patients who received HGT-1410 in Study HGT-SAN-093 and to initiate treatment to patients who received no-treatment in Study HGT-SAN-093. As such, all patients will be treated during this study; there is no control group.

In order to traverse the blood-brain barrier, HGT-1410 will be administered directly to the CNS using an IDDD or, if the IDDD is non-functional, via LP. The advantage of using an IDDD is the potential to obviate the need for multiple lumbar punctures for drug delivery. HGT-1410 will be administered through the IDDD or, if the IDDD is non-functional, via lumbar puncture.

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

4.3 Study Duration

Patients are expected to participate in this study for up to 30 months. Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

5 STUDY POPULATION SELECTION

5.1 Study Population

A maximum of 21 patients with MPS IIIA who completed Study HGT-SAN-093 are planned to enroll in this study.

5.2 Inclusion Criteria

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

1. Patient has completed through at least the Week 48 visit of Study HGT-SAN-093.
2. The patient's parent(s) or legally authorized guardian(s) has voluntarily signed an Institutional Review Board (IRB)/ ethics committee (EC)–approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

5.3 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria are met:

1. The patient, if randomized to treatment in Study HGT-SAN-093, has experienced a decline of more than 20 points in the BSID-III cognitive DQ score between Baseline and the Week 48 visit in Study HGT-SAN-093, AND, upon individual evaluation by the Investigator, has been deemed a treatment failure*.
2. The patient has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with HGT-1410, including but not limited to clinically relevant intracranial hypertension, severe infusion-related reactions after treatment with HGT-1410, uncontrollable seizure disorder.
3. The patient has a known hypersensitivity to any of the components of HGT-1410. Patients with documented infusion-related reactions that are clinically manageable (for example, with pre-medication or slowing infusion rate) are not necessarily excluded based on the assessment of the Investigator.
4. The patient is enrolled in another clinical study, other than HGT-SAN-093, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use (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's drug therapy requires substances known to be incompatible with the materials of construction.
d. The patient has a known or suspected local or general infection.
e. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
f. The patient has 1 or more spinal abnormalities that could complicate safe implantation or fixation.
g. The patient has a functioning CSF shunt device.
h. The patient has shown an intolerance to an implanted device.

7. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations or is otherwise unlikely to complete the study) as determined by the Investigator.

*All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in the BSID-III DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Investigational Product

The investigational product to be used in this study is HGT-1410, rhHNS for IT use.

The HGT-1410 drug product is a sterile solution for injection in single-use vials for IT administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, 0.02% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.

6.1.2 Intrathecal Drug Delivery Device

The drug product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S device is intended for long-term, intermittent access to the IT space for the delivery of investigational drug. The device is Conformité Européenne (CE)-marked in the European Union (EU) and investigational in non-EU countries.

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

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

Further details are provided in the SOPH-A-PORT Mini S IFU.

6.1.3 Comparator Product

Not applicable

6.2 Treatment Administered

The study drug will be administered through an IDDD. In the event of IDDD malfunction or failure, HGT-1410 may be administered via LP.

Patients who were randomized to receive HGT-1410 in Study HGT-SAN-093 will continue to have HGT-1410 administered through the IDDD that was implanted during Study HGT-SAN-093.

Patients who were randomized to no treatment in Study HGT-SAN-093 will be scheduled to undergo surgical placement of the SOPH-A-PORT Mini S device. The initial implantation and any revision and/or explantation of the SOPH-A-PORT Mini S will be performed by pediatric or general neurosurgeons or anesthesiologists who have experience in port and catheter implant

procedures and IT-access procedures and have completed training for the SOPH-A-PORT Mini S. Please refer to the IFU for further details. At least 7 days will be allowed for recovery following the placement of the IDDD before the administration of the first intrathecal dose of HGT-1410. During this time, the patient will receive standard perioperative care.

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

As previously noted, under the appropriate conditions, IT HGT-1410 may be administered at local sites rather than main sites to reduce the burden of monthly travel. This is further detailed in Section 4.1.

6.3 Selection and Timing of Dose for Each Patient

After meeting eligibility criteria, patients in Groups 1 and 2 (who received HGT-1410 in Study HGT-SAN-093) will begin treatment at Weeks 50 and 52, respectively, in Study SHP-610-201. Patients will be treated for up to 120 weeks in Study SHP-610-201, for a total cumulative exposure of 168 weeks across Studies HGT-SAN-093 and SHP-610-201.

After meeting eligibility criteria, patients who were randomized to no treatment in Study HGT-SAN-093 will be scheduled to undergo surgical placement of the SOPH-A-PORT Mini S device, as described in Section 6.2. Thereafter, these patients will be administered HGT-1410 45 mg as an IT injection either Q2W or Q4W (Groups 3A or 3B, respectively), as randomized, for up to 120 weeks.

6.3.1 Missed Doses

Patients who are scheduled to receive Q2W dosing (Groups 1 and 3A) should receive their dose of HGT-1410 every 14±3 days, and patients who are scheduled to receive Q4W dosing (Groups 2 and 3B) should receive their dose of HGT-1410 every 28±7 days. If dosing cannot be administered within the indicated time window, the dose will be considered missed, and the patient will resume their dosing schedule with the next dose of HGT-1410. The dosing schedule will not change or be reset.

6.4 Method of Assigning Patients to Treatment Groups

Patients who were randomized to no-treatment in Study HGT-SAN-093 (Group 3) will be re-randomized in a 1:1 allocation ratio to receive Q2W or Q4W dosing (Groups 3A or 3B, respectively). To help ensure balance between the dose groups with respect to age at Baseline, the randomization will be stratified by age group (≤30 months and >30 months; see Section 10.3).

Patients who were randomized to receive HGT-1410 in Study HGT-SAN-093 will remain on the same treatment regimen in Study SHP-610-201.

6.5 Blinding

This study will not be blinded.

6.6 Prior and Concomitant Medications, Therapies, and Medical/Surgical Interventions

Prior and/or concomitant therapy prohibited for all patients in this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results
- The use of medications which, in the opinion of the Investigator, would place patients at risk of bleeding complications following surgery or LP
- Any other investigational therapy (drug or device) at any time during the study
- Hematopoietic stem cell or bone marrow transplant

6.7 Restrictions

6.7.1 Fluid and Food Intake

Not applicable

6.7.2 Patient Activity Restrictions

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

6.8 Treatment Compliance

Treatment with HGT-1410 will be administered via an IDDD under the supervision of the investigator and in the controlled environment of a clinical center; therefore, full patient compliance with treatment is anticipated in this study.

6.9 Packaging and Labeling

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

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 and will be in accordance with local regulatory requirements.

6.10 Storage and Accountability

6.10.1 Investigational Product

HGT-1410 will be supplied at a concentration of 15 mg/mL in single-use vials for IT administration.

HGT-1410 will be shipped by Shire or a qualified distributor to the clinical study site(s) at 2 to 8°C (36-46°F).

Drug product should be stored refrigerated (2-8°C); drug product may not be used beyond the expiration date on the vial.

The disposition of all investigational product delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the clinical trial material accountability log. The date and time of administration of the investigational 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 product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

The process for destruction of investigational product is provided in the Pharmacy Manual.

See the Pharmacy Manual for additional details.

6.10.2 Intrathecal Drug Delivery Device

The disposition of all SOPH-A-PORT Mini S devices delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the Accountability Log. The date and time of administration of the investigational product and use of the SOPH-A-PORT Mini S device must be documented on the 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 devices and return of used/unused SOPH-A-PORT Mini S device(s) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT Mini S devices are available for the monitor to inventory and prepare for product destruction or return shipment to the Sponsor or designee.

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

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

6.10.3 Comparator Product

Not applicable to this study.

7 STUDY PROCEDURES

Detailed descriptions of patient procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events for Group 1 [patients who received HGT-1410 Q2W in Study HGT-SAN-093[in Appendix 1, for Group 2 [patients who received HGT-1410 Q4W in Study HGT-SAN-093] in Appendix 2, for Group 3A [patients who received no treatment in Study HGT-SAN-093 and are randomized to receive HGT-1410 Q2W in Study SHP-610-201] in Appendix 3, and for Group 3B [patients who received no treatment in Study HGT-SAN-093 and are randomized to receive HGT-1410 Q4W in Study SHP-610-201] in Appendix 4).

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

Details for sample collection are described in the Laboratory Manual for Study SHP-610-201.

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).

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 and filing of informed consent documents should be completed according to Section 11.4.

7.2 Study Entrance Criteria

Each patient in Groups 1 and 2 (those who received HGT-1410 in Study HGT-SAN-093) will be reviewed for eligibility against the study entrance criteria prior to receiving HGT-1410 at Weeks 50 and 52, respectively.

All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

Each patient who received no treatment in Study HGT-SAN-093 (Group 3) will be reviewed for eligibility against the study entrance criteria before IDDD implantation.

Patients who do not 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.

7.3 Hearing and Vision Assessments

7.3.1 Investigator Assessment of Hearing and Vision

For patients who received no-treatment in Study HGT-SAN-093 (Group 3) only, the Investigator will use their clinical judgment to assess the patient's vision during the initial physical examination. Investigator judgment will be used to determine whether the patient's hearing and vision is adequate for cooperation with neurodevelopmental testing, as indicated in the study inclusion criteria.

7.4 Device-related Study Procedures

7.4.1 IDDD Implantation or Revision Procedures

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

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

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

7.4.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative X-ray check of the IDDD will be performed following surgery for Groups 3A and 3B to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The X-rays may be performed to check placement of the device, as needed, throughout the study. At a minimum, the date of the X-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional X-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray will be performed to assess the potential cause of malfunction. Fluoroscopy should be used during device implantation procedures.

7.4.3 CSF Sampling Procedure

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

7.4.4 Device Adjustment, Revision, or Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage using the standard administration steps detailed in the device's IFU due to a device-related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot

be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

The IDDD will then be surgically adjusted, 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.

Details of the device removal will be recorded in the patient's eCRF. Refer to the SOPH-A-PORT Mini S IFU for further details.

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, extension study, expanded access program, commercially available drug).

7.5 Investigational Product Administration

Patients will be administered HGT-1410 by means of an IDDD, either every 2 weeks (Q2W) or every 4 weeks (Q4W). 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 4 hours post-dosing and will be discharged when deemed clinically stable by the Investigator. The number of IDDD revisions/replacements is limited to 2 per patient in any 6-month period. Therefore, in the "worst case scenario" of 2 IDDD failures occurring within 1 month, up to 11 consecutive doses of HGT-1410 administered via LP will be necessary for patients in the Q2W dosing group, and up to 5 consecutive doses via LP will be necessary for patients in the Q4W dosing group until the IDDD can be revised or replaced.

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

It is expected that all or most doses of HGT-1410 will be successfully administered following the application of topical anesthetic cream to the skin overlying the IDDD access port (see IDDD Manual for details). However, in some cases, sedation or general anesthesia may be required and may be used at the discretion of the Investigator. Any sedative or anesthetic drugs used must be recorded as concomitant medications.

Intrathecal administration of investigational product will be preceded by CSF sampling for clinical laboratory analysis (cell count, protein, glucose) and storage for additional analyses which may include pharmacodynamics (GAG concentration) and analyses of HGT-1410 enzyme and anti-rhHNS antibodies, according to the relevant Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

All HGT-1410 administrations will be followed by a flush with preservative-free saline of at least 2 mL. The total volume of investigational product and flush administered is targeted

towards replenishing the volume of CSF withdrawn. If the total volume of HGT-1410 plus 2 mL saline flush is less than the total volume of CSF withdrawn, additional saline will be administered to balance the volumes withdrawn and injected.

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

7.6 Efficacy Assessments

7.6.1 Neurocognitive and Developmental Assessments

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of patient neurodevelopmental status (see Table 7-1).[11] The assessments are estimated to last between 2 and 4 hours and must be conducted prior to any invasive procedures, such as blood draws, and prior to sedation or anesthesia. Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows:

- Cognition: The BSID-III[12] will be used to assess all patients through the age of 42 months. Once patients reach age 42 months, an attempt will be made to switch the cognitive assessment to the KABC-II. If the cognitive status of the patient does not allow for testing by the KABC-II, the BSID-III may be used.
- Adaptive behaviors: The VABS-II[13] will be used to assess all patients.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments are summarized below in Table 7-1.

Table 7-1 Neurodevelopmental Assessments Tests

Cognitive Test or Scale	Developmental or Cognitive Areas of Assessment
BSID-III[12]	Summary score and sub-domains: - Cognitive - Motor - Social/Emotional - Language
KABC-II	Cognitive and processing skills
ADAPTIVE BEHAVIOR	
VABS-II[13]	Communication Daily Living Socialization Motor Skills

Abbreviations: BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; KABC-II= Kaufman Assessment Battery for Children, Second Edition; VABS-II=Vineland Adaptive Behavior Scales, Second Edition

7.6.2 Quality of Life Indicator: Infant Toddler Quality of Life Questionnaire

The ITQoL will be administered during the study. The ITQoL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well-being of the

child and assesses the quality of the parent/guardian's life. If a patient is over 5 years of age, they do not have to complete the ITQoL.

7.6.3 Health Economics and Outcomes Research: Healthcare Utilization Questionnaire

The HCUQ will be administered during the study. This HCUQ focuses on the direct and indirect costs of care for patients with MPS-III.

7.7 Magnetic Resonance Imaging

7.7.1 Head

Regional brain volumes, including total cortical gray matter volume, will be assessed through an MRI of the head. The patient will be under general anesthesia for this assessment. Instrument standardization and central analysis of MRIs will be performed by a designated contract research laboratory.

7.7.2 Liver and Spleen

Liver and spleen volumes will be assessed through an MRI, performed at the same times as for the MRI of the head. The patient will be under general anesthesia for this assessment. Instrument standardization and central analysis of MRIs will be performed by a designated contract research laboratory.

7.8 Pharmacokinetic Assessments

Blood samples will be collected for measurement of serum concentrations of HGT-1410 and determination of pharmacokinetic parameters at the times specified in the Schedules of Events (see Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 6). Additionally, CSF samples will be collected from patients who received no treatment in Study HGT-SAN-093 at the times specified in the Schedules of Events (see Appendix 3, Appendix 4, and Appendix 6). The results of these assessments will be addressed in a separate pharmacokinetics report.

Patients may be discharged from the hospital after the 24-hour blood draw. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); this will be decided in consultation with the Investigator. Patients will return to the hospital for pharmacokinetic blood and CSF sampling at the 48-hour time point. Patients will be discharged to home after the physical examination and blood draws have been completed at the 48-hour PK time point. See Appendix 6 for more details regarding timing for pharmacokinetic sample collection.

Serum and CSF pharmacokinetic collection, processing, and shipping instructions will be provided in the Laboratory Operations Manual.

7.9 Pharmacodynamic Biomarker Assessments (CSF and Urine GAG Levels)

CSF and urine samples will be obtained to measure the concentration of GAG according to the schedules of events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4). Details about CSF collection are provided in Section 7.11.5.3.

7.10 Concomitant Medications, Therapies, and Medical/Surgical Interventions

All non-protocol treatments and medications that occur from the time of informed consent through the safety follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the eCRF. Concomitant therapy includes any therapies/interventions administered to patients, and these will be recorded on the concomitant therapy eCRF. Any medical/surgical procedures performed on the patients will be recorded on the concomitant medical/surgical procedures eCRF. Concomitant medications, both prescribed and over-the-counter (including genistein and anesthesia medications) will be recorded on the concomitant medication eCRF.

Every effort should be made to keep symptomatic MPS IIIA treatment constant throughout the study. However, changes in medications are acceptable if necessary according to clinical judgment. All changes will be recorded on the appropriate eCRF. Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

7.11 Safety Assessments

7.11.1 Vital Signs

Vital signs are to be recorded on the eCRF for all patients and will include heart rate, blood pressure, respiration rate, and body temperature. Vital signs will be recorded for at least 4 hours following each dose of HGT-1410, as described in the Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

7.11.2 Physical Examination, Including Height, Weight, and Head Circumference

During the study, physical examinations will be performed at the time points indicated in the Schedules of Events. For Groups 1 and 2, full physical examinations will be conducted at Weeks 96, 120, 144, and 168, and for Groups 3A and 3B, full physical examinations will be conducted during the IDDD implantation period and at Weeks 24, 48, 72, 96, and 120. The remainder of physical examinations will be symptom-directed.

Physical examinations will include a review of the patient's general appearance, neurological examination, as well as evaluation of the body systems described in Table 7-2, including the port and catheter track. Any abnormal change in findings will be recorded as an AE on the appropriate eCRF.

Table 7-2 Assessments for Physical Examinations

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

Table 7-2 Assessments for Physical Examinations

Assessment	Assessment
Port and catheter track	

Height and weight will be recorded for all patients.

The clinical site staff will be instructed to use calibrated scales for weight measurement where possible. The same scale is to be used at the clinical site for all patients at each specified time point during the study.

Head circumference will be measured for Groups 3A and 3B during the IDDD implantation period. All data will be recorded on the eCRF.

7.11.3 Electrocardiogram

An ECG will be performed in accordance with the clinical site's standard practice(s) and are to be performed after study drug administration. Electrocardiogram recordings will be read locally at the clinical site and will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, and QT. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF. If the patient is unable to cooperate with electrocardiography, and if sedation or general anesthesia is employed during that study visit, the ECG may be performed under sedation/anesthesia.

7.11.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection. Procedures for collection and handling of samples are included in the Laboratory Manual. Blood volumes are presented in Appendix 5.

Clinical laboratory tests will include the following (see Table 7-3):

Table 7-3 List of Laboratory Tests

Hematology:

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

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Microscopic examination
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen
- Triglycerides
- Uric acid

Anti-rhHNS antibody assessment

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Creatine kinase (CK) and subtypes
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Coagulation (performed at IDDD implantation):

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

7.11.5 Cerebrospinal Fluid Assessments

Cerebrospinal fluid will be obtained from patients during surgical implantation of the IDDD (Groups 3A and 3B only), immediately prior to each injection of study drug and at the safety follow-up visit. Should the IDDD become clogged or undergo mechanical complications, the CSF sample will be obtained via LP.

The volume of CSF collected at each visit will vary according to the number of CSF assessments. The initial 1 mL of CSF aspirated via the IDDD will be discarded, to eliminate fluid in the device's "dead space." The next 1 mL of CSF will be sent to the local laboratory. Subsequently drawn CSF will be stored, depending on the requirement for that visit (see the Schedules of Events in Appendix 1, Appendix 2, Appendix 3, Appendix 4, and the Laboratory Manual). If CSF is obtained via LP, there is no need to discard the first mL of CSF, and this can be sent to the local laboratory for standard clinical assessments. If the patient is clinically stable

in the opinion of the Investigator, HGT-1410 can be administered immediately following withdrawal of CSF, without awaiting the results of the CSF clinical laboratory data.

Each CSF sample collected will have the assessments described in Sections 7.11.5.1 through 7.11.5.4. Cerebrospinal fluid sample collection, processing, and shipping instructions are provided in the Laboratory Manual. Total CSF volumes are presented in Appendix 5.

7.11.5.1 Standard CSF Safety Laboratory Assessments

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

7.11.5.2 Anti-rhHNS Antibodies and Biomarkers in CSF

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of anti-rhHNS antibody evaluation, exploratory proteomics biomarkers, and/or other CSF biomarkers.

7.11.5.3 CSF GAG Levels and Biomarkers

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of CSF GAG, GAG degradation components, HS/dermatan sulfate (DS) oligosaccharides, or other CSF markers. The CSF pharmacodynamic sample will be obtained at the same visit as a serum sample as described in Section 7.9.

7.11.5.4 [redacted]

[redacted]

7.11.6 Device Assessments

[redacted] These data will be collected on the patient's eCRF from the time of initial implantation.

7.11.7 Collection and Storage of Biological Samples for Biomarker Studies

Biomarker analyses may be performed at the Shire research laboratory or at a Shire-designated research laboratory. Collection and processing of CSF samples will be performed as specified in the Laboratory Manual. Samples will be stored securely to ensure patient confidentiality. Samples obtained for this study will be stored for up to 10 years. Thereafter, samples will be destroyed.

7.12 Sample Collection, Storage, and Shipping

Details for study procedures including sample collection are provided in the Laboratory Manual for this study.

7.13 Adverse Events Assessments

7.13.1 Definitions of Adverse Events and Serious Adverse Events

7.13.1.1 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 product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- 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 eCRF, regardless of the severity or relationship to investigational product. 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.

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.

7.13.1.2 Adverse Events Due to Systemic Exposure to HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration. Investigators will judge the relationship of AEs to the drug infusion and describe the clinical details on the AE

form. The temporal relationship of an AE to the drug infusion will be determined upon analysis of the AE and study treatment administration data.

7.13.1.3 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, 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

7.13.1.4 IDDD-related Adverse Events

IDDD 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 7.13.2.2) should not be entered as an adverse event unless it has physiological consequences. In the event of a device failure (defined in Section 7.13.2.3), the device may need to be replaced or repaired. If overnight hospitalization is required for such a procedure (or the device failure meets any other serious criteria, eg, medically important), the device failure will be reported as a serious adverse event. Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF and the serious adverse event (SAE) form (when applicable). A list of the most common IDDD AEs is included in Appendix 7.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS (FOR IT STUDIES; AMEND/DELETE SECTION AS APPLICABLE)

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 postoperative complications (such as postoperative infection). These events are related to the surgical procedure itself.

IT ADMINISTRATION PROCESS ADVERSE EVENTS

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

7.13.1.5 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered 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).

An unanticipated adverse device effect (UADE) is any SAE 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).

7.13.2 Device-associated Definitions

7.13.2.1 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.

Device adjustment: surgery that does not result in partial or full device revision (see definition above) or removal. Examples of device adjustment include surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair.

7.13.2.2 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.

7.13.2.3 Device Failure

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

7.13.3 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-4. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-4 Adverse Event Severity

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

7.13.4 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.

7.13.5 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product, device (IDDD), device surgical procedure, or IT administration process will be assessed by the Investigator based on the following definitions (see Table 7-5).

Table 7-5 Adverse Event Relatedness

Relationship	Definition
Not Related	Unrelated to investigational product, device, device surgical procedure, or IT administration process.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, the presence of

Table 7-5 Adverse Event Relatedness

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

7.13.6 Procedures for Recording and Reporting Adverse Events

7.13.6.1 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, the patient's parent(s), or the patient's legally authorized representative 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 30 days after the last dose for patients who complete the study.

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.

7.13.6.2 Reporting Serious Adverse Events

Any SAE, regardless of relationship to investigational 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 product and/or device. 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:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] (UK) OR United States FAX: [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted], DO

Email: [redacted]

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

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

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

The Investigator must promptly report all required information to the IRB/EC. It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any Council for International Organizations of Medical Sciences I/MedWatch 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/EC receives a copy of the report and that a copy is also filed within their study files.

7.14 Abuse, Overdose and Medication Error

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

Misuse – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: 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 medicinal product higher than the protocol-mandated dose. No clinical information on overdose is available.

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

All investigational medicinal product provided to pediatrics should be supervised by the parent/legally authorized representative/caregiver.

7.15 Removal of Patients from the Trial or Investigational 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 one or more study visits
- The patient was erroneously included in the study.

- The patient develops an exclusion criterion.
- The patient suffers an intolerable AE.
- The study is terminated by the Sponsor.

The patient, the patient's parent(s), or the patient's legally authorized representative 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 or the patient's parent(s) or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the safety follow-up assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. 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.

7.16 Safety-Related Study Stopping Rules

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

This study will be stopped and safety data reviewed if any patient experiences a life-threatening or fatal SAE, either of which is considered possibly or probably related to the investigational product.

Following the review of safety data, the status of the study will be one of the following:

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

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

7.17 Appropriateness of Measurements

The neurocognitive and developmental assessments planned for this study are intended to gauge the potential treatment effect and safety of 2 dose levels of HGT-1410 over time on behavioral and cognitive criteria in patients with MPS IIIA. The selection of tests used for the cognitive assessment, and the expression of results as a ratio of mental age equivalence to calendar age to generate a DQ, were developed in collaboration with clinical psychologists with expertise in the assessment of severely disabled children with neurometabolic diseases.

The BSID-III, KABC-II, and VABS-II are instruments that have been used to assess development in healthy children and those with developmental delay. Their use in this study will

contribute to their validation in patients with MPS IIIA. The utility of these measures to track disease progression has been demonstrated in Shire's natural history study of MPS IIIA (HGT-SAN-053).

The BSID-III was selected for the following reasons:

- Widespread familiarity with the instrument
- Availability of age equivalent scores for severely impaired children
- Nonverbal content (ie, on the cognitive scale on the BSID-III)
- Availability of language and motor assessment (Both are domains on the BSID-III.)

The BSID-III is validated for children through the age of 42 months. Patients are to be switched to another instrument, the KABC-II, to measure cognition after the age of 42 months. The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

The VABS-II, a parent-reported outcome, was selected as an adaptive measure for the same reasons. Of note, to maximize standardization and reduce bias, the "interview" form of the VABS-II will be administered by the clinical psychologist/psychometrist at the same time as the BSID-III assessment.

The use of age equivalent scores rather than standard scores permits the assessment of children with severe disability in whom standard scores would otherwise be insensitive to change. Given the potentially rapid progression of MPS IIIA, a child who is assessable using a standard score at baseline may rapidly decline to such an extent that the assessment "floor" is reached and further change is not measurable. Additionally, the use of age equivalence scores permits comparison and correlation between the BSID-III and VABS-II. The use of DQ yields a parameter that tracks the dynamic progression of MPS IIIA disease, as observed in Shire's natural history study.

This study will utilize standard safety assessments including AEs, vital signs, standard clinical tests, and ECGs. Antibodies against the investigational drug will also be measured.

8 STUDY ACTIVITIES

The timing of study activities are described for each of the 3 patient groups below, and in Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively for Group 1 (initially randomized to receive HGT-1410 Q2W in Study HGT-SAN-093), Group 2 (initially randomized to receive HGT 1410 Q4W in Study HGT-SAN-093), Group 3A (initially randomized to no-treatment in Study HGT-SAN-093 and randomized to HGT-1410 Q2W in Study SHP-610-201), and Group 3B (initially randomized to no-treatment in Study HGT-SAN-093 and randomized to HGT-1410 Q4W in Study SHP-610-201). Study activities for all patients are detailed in Section 7.

8.1 Group 1 (Maintaining Q2W Dosing)

8.1.1 Treatment Period (Weeks 50 through 168)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 1 will receive 45 mg HGT-1410 IT Q2W (ie, every 14±3 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

The first 48 weeks of treatment for Group 1 occurred in Study HGT-SAN-093, and therefore patients in Group 1 will begin this study at Week 50.

For patients in Group 1, HGT-1410 will be administered every other week from Week 50 through Week 168.

8.1.1.1 Pre-treatment Assessments

- Review of study eligibility and informed consent
- Full physical examination (PE), including height and weight at Weeks 72, 96, 120, 144, and 168; symptom-directed PE at all other visits
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 72, 96, 120, 144, and 168
- Quality of life (QoL) questionnaire: ITQoL for patients ≤5 years of age: Weeks 72, 96, 120, 144, and 168
- Health economics questionnaire: HCUQ: Weeks 72, 96, 120, 144, and 168
- MRIs of head, liver, and spleen: Weeks 96 and 144
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168

- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Serum pharmacokinetics sampling at Week 96 (see Appendix 6 for the pharmacokinetics collection schedule)

8.1.1.2 Post-treatment Assessments

- ECG at Weeks 96, 144, and 168
- Serum pharmacokinetics sampling at Week 96 (see Appendix 6 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.1.2 Safety Follow-up Visit: Week 172 (±7 days)

All patients will have a safety follow-up at Week 172 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.2 Group 2 (Maintaining Q4W Dosing)

8.2.1 Treatment Period (Weeks 52 through 168)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 2 will receive 45 mg HGT-1410 IT Q4W (ie, every 28±7 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

The first 48 weeks of treatment for Group 2 occurred in Study HGT-SAN-093, and therefore patients in Group 2 will begin this study at Week 52.

For patients in Group 2, HGT-1410-IT Q4W study drug will be administered Q4W from Week 52 through Week 168.

8.2.1.1 Pre-treatment Assessments

- Review of study eligibility and informed consent
- Full PE, including height and weight at Weeks 72, 96, 120, 144, and 168; symptom-directed PE at all other visits
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 72, 96, 120, 144, and 168
- QoL questionnaire: ITQoL for patients ≤5 years of age: Weeks 72, 96, 120, 144, and 168
- Health economics questionnaire: HCUQ: Weeks 72, 96, 120, 144, and 168
- MRIs of head, liver, and spleen: Weeks, 96 and 144
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Serum PK sampling at Week 96 (see Appendix 6 for the pharmacokinetics collection schedule)_

8.2.1.2 Post-treatment Assessments

- ECG at Weeks 96, 144, and 168
- Serum PK sampling at Week 96 (see Appendix 6 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.2.2 Safety Follow-up Visit: Week 172 (±7 days)

All patients will have a safety follow-up at Week 172 or 30 (±7) days after their last dose of HGT-1410:

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.3 Group 3 (Patients Randomized to No Treatment in Study HGT-SAN-093)

Patients in Group 3 received no treatment in Study HGT-SAN-093, and therefore these patients will begin this study at Day -27 to -7.

8.3.1 IDDD Implantation (Days -21 to Day -7)

8.3.1.1 Prior to IDDD Implantation

Prior to enrollment in the study, patients who were initially randomized to no treatment in Study HGT-SAN-093 will undergo the following assessments during the IDDD implantation period, prior to IDDD implantation surgery:

• Written informed consent • Assessment of eligibility according to inclusion/exclusion criteria • Vital signs • Investigator assessment of vision and hearing ability • PE, including height, weight, and head circumference • ECG	• Clinical laboratory tests, including PT and aPTT • BSID-III/KABC-II • VABS-II • ITQoL (for patients ≤5 years of age) • HCUQ • Concomitant medications, therapies, and procedures • AE monitoring

The PE, ECG, height, weight, and clinical labs (hematology, serum chemistry, and urinalysis) need to be performed within 7 days prior to the IDDD implantation surgery date. If more than 7 days elapse between the date of these assessments and the IDDD implantation surgery date, the assessments must be repeated within 7 days prior to surgery.

8.3.1.2 Day of IDDD Implantation

Surgical implantation of the IDDD includes surgical implantation of the IDDD and a post-surgical assessment. IDDD placement will require anesthesia.

Assessments to be performed on the day of IDDD implantation include:

<u>Prior to anesthesia:</u> • Symptom-directed PE • ECG (before anesthesia if possible) • Vital signs • AE monitoring • Concomitant medications, therapies, and procedures	<u>During time patient is anesthetized:</u> • If logistically possible, head, liver, and spleen MRI (before IDDD implantation) • IDDD implantation • CSF samples collected for clinical laboratory analysis (chemistry, cell count), CSF GAG, CSF storage for biomarkers • <u>Postoperative:</u> X-ray to check IDDD placement

8.3.2 Postoperative Check – Days 1 to 3

The postoperative check can occur anytime 1 to 3 days after IDDD implantation. Assessments include postoperative check of the IDDD incision; vital signs; symptom-directed PE; concomitant medications, therapies, and procedures; and AE monitoring.

8.3.3 Randomization (Can Occur Any Time After Meeting Study Entry Criteria)

All patients in Group 3 (patients who were initially randomized to no treatment in Study HGT-SAN-093) will be randomized in a 1:1 allocation ratio to receive Q2W or Q4W dosing (Groups 3A or 3B, respectively), as described in Section 6.4.

8.4 Group 3A (Initiating HGT-1410 Q2W Dosing)

8.4.1 Treatment Period (Weeks 0 through 120)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 3A will receive 45 mg HGT-1410 IT Q2W (ie, every 14±3 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

For patients in Group 3A, HGT-1410 will be administered every other week from Week 0 through Week 120.

8.4.1.1 Pre-treatment Assessments

- Full PE, including height and weight at Weeks 24, 48, 72, 96, and 120; symptom-directed PE at all other visits.
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 24, 48, 72, 96, and 120
- QoL questionnaire: ITQoL for patients ≤5 years of age: Weeks 24, 48, 72, 96, and 120
- Health economics questionnaire: HCUQ: Weeks 24, 48, 72, 96, and 120
- MRIs of head, liver, and spleen: Weeks 24, 48, and 96
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, and 120
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120

- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 6 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 6 for the pharmacokinetics collection schedule)

8.4.1.2 Post-treatment Assessments

- ECG at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 96, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 6 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 6 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.4.2 Safety Follow-up Visit: Week 124 (±7 days)

All patients will have a safety follow-up at Week 24 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.5 Group 3B (Initiating HGT-1410 Q4W Dosing)

8.5.1 Treatment Period (Weeks 0 through 120)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 3B will receive 45 mg HGT-1410 IT Q4W (ie, every 28±7 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

For patients in Group 3B, HGT-1410 will be administered Q4W from Week 0 through Week 120.

8.5.1.1 Pre-treatment Assessments

- Full PE, including height and weight at Weeks 24, 48, 72, 96, and 120; symptom-directed PE at all other visits

- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 24, 48, 72, 96, and 120
- QoL questionnaire: ITQoL for patients ≤5 years of age: Weeks 24, 48, 72, 96, and 120
- Health economics questionnaire: HCUQ: Weeks 24, 48, 72, 96, and 120
- MRIs of head, liver, and spleen: Weeks 24, 48, and 96
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, and 120
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 6 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 6 for the pharmacokinetics collection schedule)

8.5.1.2 Post-treatment Assessments

- ECG at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 96, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 6 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 6 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment

8.5.2 Safety Follow-up Visit: Week 124 (±7 days)

All patients will have a safety follow-up at Week 24 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE 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. The training will be documented.

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 Food and Drug Administration (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 and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Statistical analysis will generally be performed by the Biometrics Department of Shire using SAS statistical software (SAS Institute, Cary, NC, USA). Analysis of any PK and health economics and outcomes data will be performed by the Shire Clinical Pharmacology and Pharmacokinetics group and the Health Economics and Outcomes Research groups, respectively. The analysis methods for all other study data (demographic and baseline characteristics, efficacy variables, and safety variables) will be detailed in the statistical analysis plan (SAP). The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial.

Any hypothesis tests will be 2-sided and will be viewed as exploratory. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

Unless otherwise indicated, all summary statistics will be presented by treatment group (either Q2W or Q4W) to which the patients were randomly assigned (for patients who were initially assigned to Q2W or Q4W group in Study HGT-SAN-093 or patients who were assigned to no-treatment in HGT-SAN-093 and were randomly assigned to Q2W or Q4W in Study SHP-601-201).

All safety data will be summarized descriptively. The change from baseline at each time point for efficacy outcomes will be summarized. Generally, the mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented. If the parametric assumption for the distribution cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference and the corresponding 95% confidence interval (ie, median difference or Hodges–Lehmann estimator and the corresponding confidence intervals). Developmental quotients will be computed as a ratio, expressed as a percentage using the age-equivalent score divided by the age at testing (ie, [age-equivalent score/chronological age] x 100). Developmental delay scores will be calculated as the age-equivalent score minus the chronological age. Additional efficacy analyses in the subgroups of patients who received treatment or no treatment in Study HGT-SAN-093 will be performed.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis. The data included for treated patients in HGT-SAN-093 starts from the baseline of Study HGT-SAN-093 and for patients who received no treatment in HGT-SAN-093 from the baseline of Study SHP-610-201. Baseline is the assessment obtained prior to the first dose of HGT-1410.

10.2 Determination of Sample Size

As this is an extension study of Study HGT-SAN-093, any patients who enrolled and completed that study are eligible to enroll in Study SHP-601-201, and no statistical estimation for sample

size calculation was performed. A maximum sample size of 21 patients in this study is expected based on the sample size in Study HGT-SAN-093.

10.3 Method of Assigning Study Subjects to Treatment Groups

Patients who were randomized to receive Q2W or Q4W dosing in Study HGT-SAN-093 (Groups 1 and 2, respectively) will maintain their assigned dosing regimen in Study SHP-610-201.

Patients who were randomized to receive no-treatment in Study HGT-SAN-093 (Group 3) will be re-randomized in a 1:1 allocation ratio via a computer-generated randomization schedule to receive Q2W or Q4W dosing regimen (Groups 3A or 3B, respectively) in Study SHP-610-201. To help ensure balance between the dose groups with respect to age at Baseline, the randomization will be stratified by age group (≤30 months and >30 months).

10.4 Population Description and Exposure

10.4.1 Analysis Populations

The population for all safety analyses will be the safety population, defined as all patients who had the IDDD implant or received at least one dose of study drug in the extension study. Safety analyses will be conducted according to the treatment received. Device related analyses will be conducted in the subset of patients in the safety population who had the device implanted.

The population for all efficacy analyses will be the intent-to-treat (ITT) population, defined as all randomized patient according to the treatment assigned.

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

10.4.2 Subject Disposition

The number of patients screened; the number and proportion of patients randomized, included in the safety population, completed the study, and discontinued prematurely will be presented in a summary table by treatment group; reasons for discontinuation/withdrawal will also be summarized.

10.4.3 Protocol Deviations

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

10.4.4 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by the individual treatment group and the overall HGT-1410 treatment group for the safety population.

10.4.5 Treatment Compliance and Extent of Exposure

The total number of doses of study drug, the number of doses received via IDDD, the number of doses received via LP, the average duration of IT administration and treatment compliance will be summarized by treatment group for the safety population.

The duration of IT administration is calculated by subtracting the IT administration start time from the IT administration end time.

Treatment compliance is defined as: [(Number of Complete IT administrations) ÷ (Expected Number of IT administrations)] * 100.

10.5 Analysis of Efficacy

The analysis of efficacy data will be based on the ITT population.

10.5.1 Primary Analysis

The primary objective of this study is to evaluate long-term safety of HGT-1410 in patients with MPS-III. Therefore the primary analysis will be discussed in the safety analysis section, Section 10.7.

10.5.2 Secondary Efficacy Analysis

10.5.2.1 Bayley Scales of Infant Development, Third Edition/Kaufman Assessment Battery for Children, Second Edition

The observed values and changes from baseline in DQ, age equivalent, and developmental delay scores for each subtest (Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor) will be summarized descriptively for each assessment time point by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean age equivalent and DQ scores for the subtests across time will be presented. A trellis plot of the age-equivalent and DQ scores within each patient will be presented. Furthermore, a spaghetti plot of the cognitive age-equivalent score against chronological age will be presented.

The KABC-II is an alternative to BSID-III. The KABC-II cognitive DQ, age-equivalent, and developmental delay scores will be combined with the corresponding BSID-III scores and summarized at each assessment time point as described above. Most of the patients will have either only BSID-III data or KABC-II data. If a patient has data obtained by each of these methods, then the method for which data is available at both baseline and post-baseline time points will be used when combining the DQ scores and age-equivalent scores.

10.5.2.2 Vineland Adaptive Behavior Scales, Second Edition

Tabular summaries of the raw scores for each domain, the average domain raw scores, the mean age equivalent score and the corresponding overall DQ scores and the corresponding change from baseline will be presented for each assessment time point by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean raw scores for the domains across time will be presented. In addition, a trellis plot of the raw scores within each patient will be presented. Similar plots will be presented for the average domain raw scores, the mean age equivalent score and the overall DQ score. A spaghetti plot of mean age equivalent score against chronological age will also be presented.

10.5.2.3 Brain MRI

Although several MRI parameters will be captured, the analysis will focus primarily on the grey matter volume, the white matter volume and the intracranial CSF volume (ventricles plus additional CSF space). The observed values and changes from baseline will be summarized for each assessment time by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean MRI parameter levels across time will be presented. In addition, Trellis plots of MRI parameters across time for each patient will be presented. A spaghetti plot of grey matter volume against chronological age will also be presented.

10.5.3 Subset Analyses

Exploratory tabular and graphical analyses as described above for efficacy endpoints will be performed both by treatment group and whether or not the patient received treatment or no treatment in Study HGT-SAN-093 (4 groups).

10.5.4 Exploratory Analyses

[redacted]

10.5.5 Analysis of Health Status

Health status will be assessed by the ITQoL. The observed value and change from baseline in ITQOL scale scores will be summarized descriptively for each assessment time by treatment group (Q2W and Q4W groups). Graphical plots of mean scores across time will be presented.

10.5.6 Analysis Health Economics and Outcomes Research

Descriptive statistics, including N, mean, median, and range (for continuous variables), and N and proportions (for categorical variables), for key HCUQ variables, including the number of

emergency room visits, caregiver employment status (FT, PT, and NW), and the number of hours of additional paid help needed by caregivers, over the course of the study. A detailed description of analyses may be provided in a separate pharmacoeconomic analysis plan.

10.6 Analysis of Pharmacokinetic and Pharmacodynamic Data

10.6.1 Pharmacokinetic Measurement and Parameters

The pharmacokinetic population will be used to perform the analysis of the pharmacokinetic data. HGT-1410 concentrations in all collected serum samples will be measured and reported. Individual patient HGT-1410 serum concentration-time profiles will be presented. Individual pharmacokinetic parameters will be derived by a noncompartmental analysis and reported. The actual pharmacokinetic blood sample collection times will be used to determine the individual patient HGT-1410 serum concentration-time profiles. Pharmacokinetic parameters will be calculated if sufficient HGT-1410 concentration-time points exist to derive values. Individual patient CSF HGT-1410 concentrations at each collection time point will be reported.

Pharmacokinetic parameters calculated will include:

- C_{max}
- t_{max}
- $AUC_{0\text{-last}}$
- $AUC_{0\text{-}\infty}$
- λ_Z
- $t_{1/2}$ calculated as $0.693/\lambda_Z$
- $CL/_F$
- V_z/F

10.6.2 Pharmacodynamic Analyses

The levels of GAG in CSF and urine are pharmacodynamic endpoints. Analyses of pharmacodynamic endpoints will be performed in the safety population.

The observed values and changes from baseline in CSF GAG levels will be summarized for each assessment time by treatment group (Q2W and Q4W group). Graphical plot(s) of mean CSF GAG levels across time will be presented. Additionally, Trellis plots of CSF GAG levels across time for each patient will be presented. Furthermore, CSF parameters will be plotted across time for each patient such that the values before and after the first instance of antibody positive status will be indicated using different colors.

The urine GAG levels will be analyzed in a manner similar to that described for CSF data.

10.7 Analysis of Safety

All analyses of safety data will be descriptive and based on the Safety population.

10.7.1 Adverse Events

Once the patient has signed the informed consent form, AEs will be recorded throughout the study and at early termination. AEs will be coded using Medical Dictionary for Regulatory Affairs (MedDRA).

Treatment-emergent AEs, defined as all AEs from the time of initial IDDD implantation (or first dose if no IDDD implant), to the safety follow-up visit, defined as the last patient visit in the study, will be summarized. For each treatment group, the number and percentage of patients having an AE and the number of events, by system organ class (SOC) and preferred term will be presented. Treatment-emergent AEs will also be summarized by severity and degree of relationship to study drug. In the case of multiple occurrences of the same AE (at the preferred term level) in an individual patient, the AE that is classified as the most severe (ie, maximum severity) will be identified for the analysis by severity and the AE that has the closest relationship to study drug/procedure will be identified for the analysis by relationship. In general, an AE will be considered a treatment-emergent AE if it cannot be definitively categorized otherwise by documentation that its onset preceded either IDDD surgery or first dose.

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

10.7.1.1 Investigational Product

Treatment-emergent AEs deemed by the investigator to be related to HGT-1410 will be summarized by presenting the number and percentage of patients having an AE and the number of events, by SOC and preferred term.

10.7.1.2 IDDD and Surgical Procedure–related AEs

Intrathecal drug delivery devices and procedure-related AEs will be summarized within MedDRA SOC by preferred term. Separate tabulations will be provided for AEs related to the IDDD, device surgical procedure, and IT administration process.

Intrathecal drug delivery device and procedure related events will be analyzed in the subset of patients in the safety population who underwent surgery for IDDD implantation.

10.7.2 Clinical Laboratory Evaluation

The measurements of each laboratory parameter (serum chemistry, hematology, urinalysis and CSF) and the corresponding normal ranges will be converted to Standard International (SI) units, if needed.

Observed values and changes from baseline for continuous laboratory test results will be summarized for each assessment time from baseline. Each laboratory result will be categorized as a patient having had (1) an abnormal and clinically significant (CS) value at any time post-baseline, (2) no CS values at any time post-baseline, but had at least 1 abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time post-baseline; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any

time post-baseline that was not CS at baseline (or the most recent non-missing value prior to the start of the treatment), their entire profile for that particular laboratory parameter will be presented as a listing.

If more than one laboratory result is reported per assessment time per parameter, the last non-missing result will be selected for analysis.

10.7.3 ECG Evaluations

The observed values and changes from baseline for continuous variables will be summarized for each assessment time by treatment group. Categorical variables, ie, sinus rhythm and atrial/ventricular hypertrophy, will be summarized in terms of number and percentage of patients in each response category for each assessment time from baseline.

10.7.4 Vital Signs

The observed values and changes from baseline for IT-administration vital signs parameters will be summarized by treatment group. The IT-administration vital signs will also be presented in a trellis plot so that the vital signs data for each IT-administration within a patient will be presented on a single page.

10.7.5 Anti-rhHNS Antibody in Serum and CSF

Serum and CSF anti-rhHNS antibody status (ie, positive or negative) at each assessment time from baseline will be summarized in terms of counts and proportion for the treatment groups. Additionally, semi-logarithmic plot of serum and CSF anti-rhHNS antibody titers across the study visits in the patients exhibiting seropositivity will also be presented.

10.7.6 Concomitant Medications

Concomitant medications will be coded using the WHO-DD. The concomitant medications that occur from the time of the surgery for IDDD implantation to the safety follow-up visit, defined as the last patient visit in the study, will be summarized by therapeutic class and preferred term.

10.7.7 Other Observations Related to Safety

10.7.7.1 IDDD Performance

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

The proportion of patients with at least 1 device failure and/or malfunction, as well as the number of and reasons for device failures/malfunctions will be summarized. The rate of device failures/malfunctions and 95% confidence interval will also be estimated. The time from initial implant surgery to first device failure and/or malfunction will be summarized. Patients without a device failure/malfunction will be censored at their last study drug injection date. A by-patient listing of the device failure/malfunction data will be displayed.

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

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

No statistical modeling or covariate adjustment is planned due to the small sample size.

10.8.2 Handling of Dropouts or Missing Data

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

10.8.3 Interim Analyses and Data Monitoring

No formal interim analysis or interim statistical testing for early stopping of the trial is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting or general study planning purposes. An independent DMC will be established to provide an ongoing, independent review and assessment of patient data, and to safeguard the interests and safety of the participating patients in the study (see Section 11.8). An analysis of the data for DMC review will occur at specific times during the study as specified in the DMC charter. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.

10.8.4 Multicenter Studies

Data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. In order to maintain desirable level of inter-rater reliability for BSID-III/KABS-II and VABS-II assessments/interviews, standardized training of the raters and parents will be conducted. Furthermore, a central reader will evaluate all MRI data.

10.8.5 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed.

10.8.6 Sensitivity Analyses

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

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

11.2 Institutional Review Board or Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/EC 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.

The protocol and any applicable documentation will be submitted or notified to the relevant Regulatory Authorities in accordance with the regulations of the countries involved in the trial.

Status reports must be submitted to the IRB/EC at least once per year. The IRB/EC must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/EC. 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/EC, including a list of all reports and documents submitted. Adverse events that are reported to the US FDA (Investigational New Drug/UADE Safety Reports) or other regulatory agencies must be submitted promptly to the IRB/EC.

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

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

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the 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).

After reading the informed consent document, the patient or 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, 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 or 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 of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorized representative. 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 or 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 patient initials will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. 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/EC, 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

11.7.1 Case Report Forms

Case report forms (paper or electronic) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original 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 resigning the eCRF.

11.7.2 Critical Documents

Before Shire initiates the trial (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 12 months of study initiation)
- Copy of Investigator and sub-Investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/EC clearly identifying the documents reviewed by name, number and date of approval or regarding approval: protocol, any amendments, Patient Information/Informed Consent Form, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB-/EC-approved Patient Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/EC Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-Investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

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

11.8 Data Monitoring Committee

An independent DMC will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study. The DMC will consist of a biostatistician and 2 clinical experts.

It is anticipated that there will be scheduled meetings annually during the conduct of the study. The first meeting will be an orientation meeting and will take place prior to the start of the study. Subsequent meetings will occur at specific times during the study as specified in the DMC charter. The final meeting will be conducted when all patients have completed the study for a comprehensive safety overview of the study. A special DMC meeting will be convened if the safety-related study stopping rules are met (see Section 7.16).

The DMC will adhere to a prospectively determined charter, which will be written by Shire and approved by the DMC. The charter will define the responsibilities of the DMC and Shire, describe the conduct of the meetings and define the data sets to be reviewed. The DMC will also be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter.

The DMC will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC 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/EC 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/EC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/EC 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/EC. 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 will be granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to

discuss the planned course of action. Any departures from the protocol must be fully documented 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/EC.

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

11.11 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable 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 product may be made at any time. Conditions that may warrant termination of the study or site include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the 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/EC, or the Sponsor (or its designee) may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.13 Data Generation and Analysis

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

Adverse events and medical history 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 and safety parameters.

11.14 Retention of Data

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

11.15 Financial Disclosure

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

11.16 Publication and Disclosure Policy

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

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

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

Shire may perform analyses of interim or final locked study data for purposes of publication.

12 LIST OF REFERENCES

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Appendix 1 Study Schedule of Events for Group 1: Maintaining HGT-1410 Q2W

Procedure	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				Follow-up
	Weeks[a]																				
	50	52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	122, 124, 126, 128, 130	132	134, 136, 138, 140, 142	144	146, 148, 150, 152, 154	156	158, 160, 162, 164, 166	168	172[h]
Informed consent	•																					
Review of inclusion/exclusion criteria	•																					
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Full PE including height, weight, and head circumference					•				•				•				•				•	
Symptom-directed PE	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/KABC-II[c]					•				•				•				•				•	
VABS-II					•				•				•				•				•	
ITQoL[d]					•				•				•				•				•	
HCUQ					•				•				•				•				•	
ECG[e]									•								•				•	
Hematology			•		•		•		•		•		•		•		•		•		•	•
Serum chemistry			•		•		•		•		•		•		•		•		•		•	•
Urinalysis			•		•		•		•		•		•		•		•		•		•	•
MRI of the head									•								•					
MRI of liver and spleen									•								•					
HGT-1410 administration	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing			•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[g]									•													
CSF sample for storage for biomarkers	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, and procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Procedure	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																			Follow-up
	Weeks[a]																			
	50	52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	122, 124, 126, 128, 130	132	134, 136, 138, 140, 142	144	146, 148, 150, 152, 154	156	158, 160, 162, 164, 166	168	172[h]

Abbreviations: Ab=antibody; AE=adverse event; aPTT= activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; ECG=electrocardiogram; GAG= glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life Questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs during the treatment period will be obtained immediately prior to IT dosing.

[c] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[d] For patients ≤5 years of age

[e] ECGs are to be performed after study drug administration.

[f] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[g] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[h] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 172.

Appendix 2 Study Schedule of Events for Group 2: Maintaining HGT-1410 Q4W

Procedure	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																					Follow-up
	Weeks[a]																					
	52	56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124, 128	132	136, 140	144	148, 152	156	160, 164	168	172[a]
Informed consent	•																					
Review of inclusion/exclusion criteria	•																					
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Full PE including height, weight, and head circumference					•				•				•				•				•	
Symptom-directed PE	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/KABC-II[c]					•				•				•				•				•	
VABS-II					•				•				•				•				•	
ITQoL[d]					•				•				•				•				•	
HCUQ					•				•				•				•				•	
ECG[e]									•								•				•	
Hematology			•		•		•		•		•		•		•		•		•		•	•
Serum chemistry			•		•		•		•		•		•		•		•		•		•	•
Urinalysis			•		•		•		•		•		•		•		•		•		•	•
MRI of the head									•								•					
MRI of liver and spleen									•								•					
HGT-1410 administration	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing			•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[g]									•													
CSF sample collection for storage for biomarkers	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, and procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; con meds=concomitant medications; ECG=electrocardiogram; GAG= glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PD=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human

Procedure	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																				Follow-up
	Weeks[a]																				
	52	56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124, 128	132	136, 140	144	148, 152	156	160, 164	168	172[a]

heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs during the treatment period will be obtained immediately prior to IT dosing.

[c] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[d] For patients ≤5 years of age

[e] ECGs are to be performed after study drug administration.

[f] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[g] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[h] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 172.

Appendix 3 Study Schedule of Events for Group 3A: Initiating HGT-1410 Q2W

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
Procedure	**Days**		**Weeks[a]**																																						
	-21 to -7	**Postop check**	**Day 0 Week 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50, 52, 54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102, 104, 106**	**108**	**110, 112, 114, 116,118**	**120**	**124[l]**
Informed consent	•																																						
Review of inclusion/exclusion criteria	•																																						
Randomization	•																																						
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigator assessment of vision and hearing ability	•																																						
Full PE including height, weight, and head circumference	•[c]														•												•				•				•				•	
Symptom-directed PE		•	•	•	•	•	•	•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•	•		•	•	•		•	•	•		•	•		•
BSID-III/KABC-II[d]	•[e]														•												•				•				•				•	
VABS-II	•[e]														•												•				•				•				•	
ITQoL[f]	•[e]														•												•				•				•				•	
HCUQ	•[e]														•												•				•				•				•	
ECG[g]	•		•		•		•		•		•		•		•												•								•				•	
Hematology	•		•		•		•		•		•		•		•						•						•		•		•		•		•				•	•
PT and aPTT	•																																							
Serum chemistry	•		•		•		•		•		•		•		•						•						•		•		•		•		•				•	•
Urinalysis	•		•		•		•		•		•		•		•						•						•		•		•		•		•				•	•
MRI of the head	•[h]														•												•								•					
MRI of liver and spleen	•[h]														•												•								•					

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																			Follow-up
Procedure	**Days**		**Weeks[a]**																																				
	-21 to -7	Postop check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]
IDDD implantation	•																																						
X-ray to check IDDD placement	•																																						
Postoperative check of IDDD incision		•[i]																																					
HGT-1410 administration			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing	•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•						•						•						•		•		•		•		•		•	
Serum PK sampling[k]			•																								•							•					
CSF PK sampling[k]			•																								•												
CSF sample for storage for biomarkers	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, and procedures	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; ECG=electrocardiogram; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life Questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PD=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
Procedure	Days		Weeks[a]																																						
	-21 to -7	Postop check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]

Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs at Weeks 0-48 will be obtained immediately prior to IT dosing; at 15, 30, 45, 60, 90, and 120 minutes; and at 2.5, 3, and 4 hours after dosing. Vital signs at Weeks 50-120 will be obtained immediately prior to IT dosing.

[c] Head circumference will be measured only at screening.

[d] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[e] Cognitive assessments are to be performed before IDDD implantation. The Week 48 assessments from Study HGT-SAN-093 will be used as the baseline assessments in Study SHP-610-201. If the Week 48 assessments from Study HGT-SAN-093 are missing, these assessments will need to be performed prior to IDDD implantation in the extension study.

[f] For patients ≤5 years of age

[g] ECGs are to be performed after study drug administration.

[h] If scheduling does not permit the MRI assessments to be performed during IDDD implantation (under the same general anesthetic), then these procedures should be done before the first dose of HGT-1410 at Day -1. This would require administration of anesthesia.

[i] Postoperative check of IDDD incision (1-3 days after operation) along with con med, therapies, and procedures and AE monitoring.

[j] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[k] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection. CSF PK samples to be obtained immediately prior to IT injection, then at 4 and 48 hours following completion of the IT injection.

[l] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 124.

Appendix 4 Study Schedule of Events for Group 3B: Initiating HGT-1410 Q4W

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	**Days**		**Weeks[a]**																				
	-21 to -7	Postop check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[i]
Informed consent	•																						
Review of inclusion/ exclusion criteria	•																						
Randomization	•																						
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigator assessment of vision and hearing ability	•																						
Full PE including Height, Weight, and Head Circumference	•[c]						•				•				•				•				•	
Symptom-directed PE		•	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/ KABC-II[d]	•[e]						•				•				•				•				•	
VABS-II	•[e]						•				•				•				•				•	
ITQoL[f]	•[e]						•				•				•				•				•	
HCUQ	•[e]						•				•				•				•				•	
ECG[g]	•		•	•	•	•	•				•								•				•	
Hematology	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
PT and aPTT	•																							
Serum chemistry	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
Urinalysis	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
MRI of the head	•[h]						•				•								•					
MRI of liver and spleen	•[h]						•				•								•					
IDDD implantation	•																							
X-ray to check IDDD placement	•																							
Postoperative check of IDDD incision		•[i]																						

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	**Days**		**Weeks[a]**																				
	-21 to -7	Postop check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[f]
HGT-1410 administration			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing	•		•	•	•	•	•	•	•	•	•		•		•		•		•		•		•	
Urine sample for GAG			•	•	•	•	•	•	•	•	•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•	•	•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[k]			•								•								•					
CSF PK sampling[k]			•								•													
CSF sample collection for storage for biomarkers	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, & procedures	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse event monitoring	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; ECG=electrocardiogram; GAG= glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life Questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PD=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs at Weeks 0-48 will be obtained immediately prior to IT dosing; at 15, 30, 45, 60, 90, and 120 minutes; and at 2.5, 3, and 4 hours after dosing. Vital signs at Weeks 50-120 will be obtained immediately prior to IT dosing.

[c] Head circumference will only be measured at screening.

[d] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[e] Cognitive assessments are to be performed before IDDD implantation. The Week 48 assessments from Study HGT-SAN-093 will be used as the baseline assessments in Study SHP-610-201. If the Week 48 assessments from Study HGT-SAN-093 are missing, these assessments will need to be performed prior to IDDD implantation in the extension study.

[f] For patients ≤5 years of age

[g] ECGs are to be performed after study drug administration.

[h] If scheduling does not permit the MRI assessments to be performed during IDDD implantation (under the same general anesthetic), then these procedures should be done

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	Days		Weeks[a]																				
	-21 to -7	Postop check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[l]

before the first dose of HGT-1410 at Day -1. This would require administration of anesthesia.

i Postoperative check of IDDD incision (1-3 days after operation) along with con med, therapies, and procedures and AE monitoring.

j CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

k Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection. CSF PK samples to be obtained immediately prior to IT injection, then at 4 and 48 hours following completion of the IT injection.

l If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments done at Week 124.

Appendix 5 Blood and CSF Volumes

	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				**Follow-up**	**TOTAL**
	Weeks																					
Procedure	**50**	**52, 54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102, 104, 106**	**108**	**110, 112, 114, 116, 118**	**120**	**122, 124, 126, 128, 130**	**132**	**134, 136, 138, 140, 142**	**144**	**146, 148, 150, 152, 154**	**156**	**158, 160, 162, 164, 166**	**168**	**172**	
CSF (mL)																						
Standard CSF safety labs	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
CSF sample for GAG testing			a		a		a		a		a		a		a		a		a		a	
Anti-rhHNS Ab testing (CSF)			b		b		b		b		b		b		b		b		b		b	
CSF for storage (for biomarkers and Ab testing)	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
Total CSF Volume	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**660**
Blood (mL)																						
Hematology			2		2		2		2		2		2		2		2		2		2	2
Serum chemistry			2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.5
Anti-rhHNS Ab testing (serum)			4		4		4		4		4		4		4		4		4		4	
Serum PK sampling									9													
Total Blood Volume			**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**	**4.5**	**98.5**

Abbreviations: Ab=antibody; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; PK=pharmacokinetics; rhHNS=recombinant human heparan N sulfatase

[a] CSF for GAGs included in CSF storage sample

[b] Anti-rhHNS Ab testing in CSF will be performed on stored samples.

	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																				**Follow-up**	**TOTAL**
	Weeks																					
Procedure	**52**	**56**	**60**	**64, 68**	**72**	**76, 80**	**84**	**88, 92**	**96**	**100, 104**	**108**	**112, 116**	**120**	**124, 128**	**132**	**136, 140**	**144**	**148, 152**	**156**	**160, 164**	**168**	**172**	
CSF (mL)																							
Standard CSF safety labs	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
CSF sample for GAG testing			a		a		a		a		a		a		a		a		a		a		
Anti-rhHNS Ab testing (CSF)			b		b		b		b		b		b		b		b		b		b		
CSF for storage (for biomarkers and Ab testing)	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
Total CSF Volume	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**		**330**
Blood (mL)																							
Hematology			2		2		2		2		2		2		2		2		2		2	2	
Serum chemistry			2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.5	
Anti-rhHNS Ab testing (serum)			4		4		4		4		4		4		4		4		4		4		
Serum PK sampling									9														
Total Blood Volume			**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**	**4.5**	**98.5**

Abbreviations: Ab=antibody; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; PK=pharmacokinetics; rhHNS=recombinant human heparan N sulfatase

a CSF for GAGs included in CSF storage sample

b Anti-rhHNS Ab testing in CSF will be performed on stored samples.

	IDDD Implantation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up	TOTAL
Procedure	**Days**		**Weeks**																																					
	-21 to -7	**Postop check**	**Day 0, Week 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50, 52, 54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102, 104, 106**	**108**	**110, 112, 114, 116, 118**	**120**	**124**	
CSF (mL)																																								
Standard CSF safety labs	3		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
CSF sample for GAG testing	a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		
Anti-rhHNS Ab testing (CSF)			b		b		b		b						b						b						b		b		b		b		b		b		
CSF PK sampling (Appendix 6)			4																								4												
CSF for storage (for biomarkers and Ab testing)	8		8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
Total CSF Volume	**11**		**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**		**690**
Blood (mL)																																							
Hematology	2		2		2		2		2		2		2		2						2						2		2		2		2		2		2	2	
Serum chemistry	2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						2.5						2.5		2.5		2.5		2.5		2.5		2.5	2.5	
PT and aPTT (coagulation)	1.8																																						
Anti-rhHNS Ab testing (serum)			4		4		4		4						4						4						4		4		4		4		4		4		
Serum PK sampling (Appendix 6)			9																								9						9						
Total Blood Volume	**6.3**		**17.5**		**8.5**		**8.5**		**8.5**		**4.5**		**4.5**		**8.5**						**8.5**						**17.5**		**8.5**		**8.5**		**8.5**		**17.5**		**8.5**	**4.5**	**157.3**

	IDDD Implantation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up	TOTAL
Procedure	**Days**		**Weeks**																																					
	-21 to -7	Postop check	Day 0, Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	124	

Abbreviations: Ab=antibody; aPTT=activated partial thromboplastin time; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; IDDD=intrathecal drug delivery device; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N sulfatase

[a] CSF for GAGs included in CSF storage sample

[b] Anti-rhHNS Ab testing in CSF will be performed on stored samples.

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																					Follow-up	TOTAL
Procedure	**Days**																								
	-21 to -7	**Postop check**	**Day 0, Week 0**	**4, 8**	**12**	**16, 20**	**24**	**28, 32**	**36**	**40, 44**	**48**	**52, 56**	**60**	**64, 68**	**72**	**76, 80**	**84**	**88, 92**	**96**	**100, 104**	**108**	**112, 116**	**120**	**124**	
CSF (mL)																									
Standard CSF safety labs	3		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
CSF sample for GAG testing	a		a	a	a	a	a	a	a	a	a		a		a		a		a		a		a		
Anti-rhHNS Ab testing (CSF)			b	b	b		b		b		b		b		b		b		b		b		b		
CSF PK sampling (Appendix 6)			4								4														
CSF for storage (for biomarkers and Ab testing)	8		8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
Total CSF Volume	**11**		**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**		**360**
Blood (mL)																									
Hematology	2		2	2	2	2	2		2		2		2		2		2		2		2		2	2	
Serum chemistry	2.5		2.5	2.5	2.5	2.5	2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.5	
PT and aPTT (coagulation)	1.8																								
Anti-rhHNS Ab testing (serum)			4	4	4		4		4		4		4		4		4		4		4		4		
Serum PK sampling (Appendix 5)			9								9								9						
Total Blood Volume	**6.3**		**17.5**	**8.5**	**8.5**	**4.5**	**8.5**		**8.5**		**17.5**		**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**	**4.5**	**157.3**

Abbreviations: Ab=antibody; aPTT=activated partial thromboplastin time; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; IDDD=intrathecal drug delivery device; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N sulfatase

[a] CSF for GAGs included in CSF storage sample

[b] Anti-rhHNS Ab testing in CSF will be performed on stored samples.

Appendix 6 Pharmacokinetic and Pharmacodynamic Sample Schedule

Drug Administration	PK/PD Sampling Times
	Blood Sampling
HGT-1410 IT injection	Serum PK samples will be obtained at Weeks 0, 48, and 96 for Groups 3a and 3b. Serum PK samples will be obtained at Week 96 for Groups 1 and 2. Immediately prior to IT injection (baseline), then at 0.5, 1, 2, 4, 8, 12, 24, and 48 (Day 2) hours following completion of IT injection. Patients may be discharged from the hospital after the 24-hour blood draw. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); in consultation with the Investigator. Patients will return to the hospital for PK blood sampling at the 48-hour PK time point. Patients will be discharged for home following the last (48-hour) PK time point and following the completion of their final physical examination.
	CSF Sampling
	CSF PK and PK/PD samples will be obtained at Weeks 0 and 48 for Groups 3A and 3B only. Immediately prior to IT injection (baseline), then at 4 hours and 48 hours after the completion of the IT injection. The 4-hour and 48-hour post-dose CSF samples will only be obtained if a functioning IDDD is in place. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); in consultation with the Investigator. Patients will return to the hospital for CSF sampling at the 48 hour time points.

Abbreviations: CSF=cerebrospinal fluid; IDDD=intrathecal drug delivery device; IT=intrathecal; PD=pharmacodynamics; PK=pharmacokinetics

Appendix 7 Expected SOPH-A-PORT Mini S Adverse Device Effects

Procedure-related Complications

- Components handled improperly before, during, or after implantation
- Access port implanted incorrectly
- Catheter positioned improperly
- Injection through septum performed incorrectly
- Injection of incorrect medication through access port
- Injection outside the access port into pocket or subcutaneous tissue or extravasation
- Pocket seroma, hematoma, erosion, or infection
- 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-LP, 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 8 Protocol Amendment Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol SHP-610-201 has been amended to include language to allow for patients to be dosed at local sites and reduce the burden imposed by travel, the revision of exclusion criteria on hypersensitivity, the addition of blood and CSF volumes tables, clarification on publications and interim analysis, guidance on the management of infusion/hypersensitivity reactions, change in the medical monitor contact information, and the addition of device adjustment language to capture the full scope of device manipulations that can occur throughout the trial.

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 change summary.

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: change to medical monitor contact
Section impacted by this change: Cover page
Revised Text: Medical Monitor: [redacted]~~, MD, PhD~~ [redacted], DO
Other sections impacted by this change: 7.13.6.2 Reporting Serious Adverse Events

Change: Number of maximum patients in the study increased
Section impacted by this change: Synopsis
A maximum of ~~18~~**21** patients with MPS IIIA and who completed Study HGT-SAN-093 are planned to enroll in this study.
Other sections impacted by this change: 5.1 Study Population, 10.2 Determination of Sample Size

Change: Exclusion criteria revised
Section impacted by this change: Synopsis
The patient has a known hypersensitivity to any of the components of HGT 1410. **Patients with documented infusion-related reactions that are clinically manageable (for example, with pre-medication or slowing infusion rate) are not necessarily excluded based on the assessment of the Investigator.**
Other sections impacted by this change: 5.3 Exclusion Criteria

Change: Inclusion of language to allow for patients to be dosed at local sites
Section impacted by this change: 4.1 Overall Study Design and Plan
The Sponsor and Principal Investigator will consider the feasibility of transitioning the patient's IT dosing to local sites to reduce the burden imposed by travel. The

local sites will be selected and approved by the Sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: The main site may serve as a local site as needed, and in this case, the main site will follow the assessment schedule for a local site). The qualification requirements for physicians at local sites will be identical to those for the main sites. Local sites will be experienced with IT administration via an IDDD. For patients who were in the no-treatment group in the HGT-SAN-093 study, initial IT administrations will be at the main study site following IDDD implantation until in the opinion of the Principal Investigator there are no safety or medical concerns precluding the patient from transitioning. Patients will be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the Investigator. Exceptions include the IT injections of HGT-1410 when scheduled study assessments are scheduled; these will take place at the main site. Patients that have already received IT drug administration at the main study site would be eligible to transfer to a local site starting at Week 50 (Group 1) or Week 52 (Group 2) in SHP-610-201 if in the opinion of the Principal Investigator there are no safety or medical concerns precluding the patient from transitioning.
Other sections impacted by this change: 6.2 Treatment Administered

Change: Title of Section 7.4.4 revised
Section impacted by this change: 7.4.4 Device Revision or Removal
Device **Adjustment,** Revision, or Removal
Other sections impacted by this change: N/A

Change: Management of Infusion/hypersensitivity reactions
Section impacted by this change: 7.13.1.3 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, 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
Other sections impacted by this change: N/A

Change: Definition of device adjustment
Section impacted by this change: 7.13.2.1 Device Revision (Partial and Full)
Device adjustment: surgery that does not result in partial or full device revision (see definition above) or removal. Examples of device adjustment include surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair.
Other sections impacted by this change: N/A

Change: Clarification on publications and interim analysis
Section impacted by this change: 11.16 Publication and Disclosure Policy
Shire may perform analyses of interim or final locked study data for purposes of publication.
Other sections impacted by this change: N/A

Change: Addition of Appendix 5 – blood and CSF volumes tables
Section impacted by this change: Appendix 5
N/A
Other sections impacted by this change: N/A

Appendix 9 Protocol Signature Page

Study Title: An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease

Study Number: SHP-610-201

Final Date: 17 December 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

[redacted] [redacted]
Signature **Date**

[redacted], DO
Printed Name

Clinical Trial Protocol: SHP-610-201

Study Title:	An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease
Study Number:	SHP-610-201
Study Phase:	IIb
Product Name:	HGT-1410
Device Name:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
IND Number:	102165
EUDRACT Number	2014-003960-20
Indication:	Long-term Treatment of Mucopolysaccharidosis Type IIIA (MPS IIIA or Sanfilippo Syndrome Type A)
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc.
Sponsor Contact:	300 Shire Way Lexington, MA 02421 USA +1-617-349-0200
Medical Monitor:	[redacted], DO

	Date
Original Protocol:	23 September 2014
Amendment 1:	17 December 2015
Amendment 2:	25 January 2017

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc. (Shire)

Name of Finished Product:

HGT-1410 (Recombinant Human Heparan N Sulfatase, or rhHNS)

Name of Device:

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

Study Title:

An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease

Study Number:

SHP-610-201

Study Phase: IIb

Investigational Product, Dose, and Mode of Administration:
HGT-1410 at a dose of 45 mg administered every 2 weeks (Q2W) or 45 mg administered every 4 weeks (Q4W). HGT-1410 will be administered intrathecally (IT) by an indwelling IT drug delivery device (IDDD).

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-1410 indicated for intrathecal delivery intermittently over a long period of time.

Comparator, Dose, and Mode of Administration:

Not applicable

Primary Objective(s):

To evaluate long-term safety in patients with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo syndrome type A) who received HGT-1410

Secondary Objective(s):

To evaluate:

- The long-term cognitive function as measured by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II), age-equivalent and developmental quotient (DQ) scores in patients with MPS IIIA who received HGT-1410
- The long-term adaptive behavioral function, assessed by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) in patients who received HGT-1410
- The total cortical grey matter volume, as assessed by volumetric magnetic resonance imaging (MRI) of the brain, in patients who received HGT-1410

Exploratory Objective:

[redacted]

Pharmacokinetic and Pharmacodynamic Objectives

To evaluate:

- The pharmacokinetics of HGT-1410 in serum
- The pharmacokinetics of HGT-1410 in cerebrospinal fluid (CSF), in patients who received no treatment in Study HGT-SAN-093
- The concentration of glycosaminoglycans (GAG) in CSF and urine in patients who received HGT-1410

Health Status Objective

To evaluate health status as measured by the Infant Toddler Quality of Life Questionnaire™ (ITQoL) instrument in patients who received HGT-1410

Health Economics and Outcomes Research Objectives

To evaluate healthcare resource utilization, as evaluated by the Healthcare Utilization Questionnaire (HCUQ), in patients who received HGT-1410

Study Endpoints:

Safety evaluations include the assessment of adverse events (AEs), IDDD-related issues, laboratory values, anti-rhHNS antibody development, vital signs, physical examination findings, and electrocardiogram (ECG) results.

The secondary endpoints of this study are:

- The change from Baseline in BSID-III or KABC-II age-equivalent, DQ, and developmental delay scores
- The change from Baseline in adaptive behavioral function domains, assessed by VABS II, using raw scores, age-equivalent scores, and DQ scores
- The change from Baseline in total cortical grey matter volume, as assessed by MRI

[redacted]

The pharmacokinetic endpoint is to determine the pharmacokinetic behavior of HGT-1410 in serum. The pharmacokinetic behavior of HGT-1410 in CSF will also be determined in patients who received no treatment in Study HGT-SAN-093.

The pharmacodynamic endpoint is to determine the GAG concentrations in CSF and urine.

The health status endpoint is the ITQoL scores at each assessment time and the corresponding change from Baseline.

The health economic and outcome research endpoints evaluate key HCUQ variables, such as the number of emergency room visits, caregiver employment status (full-time, part-time, or not working), and the number of hours of additional paid help needed by caregivers over the course of the study.

Study Population:
A maximum of 21 patients with MPS IIIA and who completed Study HGT-SAN-093 are planned to enroll in this study.

Study Design:
This is an open-label study for patients who completed through at least the Week 48 Visit of Study HGT-SAN-093. Patients who originally received HGT-1410 in Study HGT-SAN-093 will remain on the same dosing regimen as they received in Study HGT-SAN-093; Group 1 will receive HGT-1410 Q2W and Group 2 will received HGT-1410 Q4W. Patients in Groups 1 and 2 will begin treatment at Week 50 and Week 52, respectively, of this extension study (Study SHP-610-201). Patients who originally received no treatment in Study HGT-SAN-093 (Group 3) will receive an IDDD following informed consent and will be re-randomized in a 1:1 allocation ratio to receive HGT-1410 via a Q2W or Q4W dosing regimen (Groups 3A and 3B, respectively) in Study SHP-610-201. Patients in Groups 3A and 3B will begin treatment on Week 0 of the extension study.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all IT injections of HGT-1410. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual(s), which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug may be administered and CSF sampled by lumbar puncture (LP). General anesthesia or sedation may be required for injections of study drug and some evaluations and can be used at the discretion of the Investigator. Patients should have the IDDD removed when they discontinue from or complete the treatment period of the study, unless the investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of the treatment period of Study SHP-610-201. For patients who received HGT-1410 in Study HGT-SAN-093, a serum pharmacokinetic sample will be obtained at the Week 96 visit (after approximately 2 full years of exposure to HGT-1410 across Study HGT-SAN-093 and SHP-610-201). For patients who received no treatment in Study HGT-SAN-093, serum pharmacokinetic samples will be obtained at the Week 0, 48, and 96 visits, and CSF pharmacokinetic samples will be obtained at the Week 0 and 48 visits in Study SHP-610-201.

Patients who do not have the IDDD removed (partial or full device) at the end of the treatment period will continue to be observed during a safety follow-up period with visits at the site every 6 months to evaluate patient safety of the device until the IDDD has been fully explanted.

Study Duration:

Approximately 30 months of treatment with HGT-1410 will occur during the study. Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no-treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

For those patients with a partial or full device still in place after completion of the treatment period, patients may be followed for safety up to an additional 3 years or until the device is removed in the last patient.

The LPLV will be the safety follow-up visit after the final device (partial and/or full) is removed from the last patient during the safety follow-up period.

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

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

1. Patient has completed through at least the Week 48 visit of Study HGT-SAN-093.
2. The patient's parent(s) or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/ethics committee–approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

Exclusion Criteria:

Patients will be excluded from the study if any of the following criteria are met:

1. The patient, if randomized to treatment in Study HGT-SAN-093, has experienced a decline of more than 20 points in the BSID-III cognitive DQ score between Baseline and the Week 48 visit in Study HGT-SAN-093, AND, upon individual evaluation by the Investigator, has been deemed a treatment failure*.
2. The patient has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with HGT-1410, including but not limited to clinically relevant intracranial hypertension, severe infusion-related reactions after treatment with HGT-1410, or uncontrollable seizure disorder.
3. The patient has a known hypersensitivity to any of the components of HGT-1410. Patients with documented infusion-related reactions that are clinically manageable (for example, with pre-medication or slowing infusion rate) are not necessarily excluded based on the assessment of the investigator.
4. The patient is enrolled in another clinical study, other than HGT-SAN-093, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use, including:
    a. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device.
    b. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator.
    c. The patient's drug therapy requires substances known to be incompatible with the materials of construction.
    d. The patient has a known or suspected local or general infection.
    e. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
    f. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation.

g. The patient has a functioning CSF shunt device.
h. The patient has shown an intolerance to an implanted device.

7. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations or is otherwise unlikely to complete the study) as determined by the Investigator.

*All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in the BSID-III DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

Efficacy Assessments:

Efficacy variables to be assessed will include cognitive function expressed as a DQ assessed by neurocognitive testing using the BSID-III/KABS-II; adaptive behavioral function over time, assessed by VABS-II; the total cortical grey matter volume and liver and spleen size as assessed by MRI; quality-of-life score (assessed using the ITQoL); and health care resource utilization (assessed using the HCUQ).

Pharmacokinetic Assessments:

The determination of HGT-1410 concentration in serum for all patients and in CSF for patients who received no treatment in Study HGT-SAN-093.

Pharmacodynamic Assessments:

The determination of GAG concentrations in CSF and urine

Safety Assessments:

Safety will be assessed during the study by the following:

- Collection of AEs (by type, severity, and relationship to treatment [HGT-1410, the IDDD, device surgical procedure, or IT administration process])
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Physical examination
- Vital signs
- Twelve-lead ECG recordings
- CSF laboratory parameters (chemistries, cell counts)
- Anti-rhHNS antibodies in CSF and serum, including determination of antibodies having enzyme neutralizing activity

Statistical Methods:

The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial. Any hypothesis tests will be 2-sided and will be viewed as exploratory. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of

patients will be available for analysis. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time, as appropriate.

Unless otherwise indicated, all summary statistics will be presented by treatment group (either Q2W or Q4W) to which the patients were randomly assigned (patients who were initially assigned to Q2W or Q4W group in Study HGT-SAN-093 or patients who received no-treatment in Study HGT-SAN-093 and were randomly assigned to Q2W or Q4W in Study SHP-610-201). Additional analyses in the subgroup of patients who received no-treatment in Study HGT-SAN-093 may be performed.

All safety data will be summarized descriptively. The change from baseline at each time point for efficacy outcomes will be summarized. Generally, the mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented. Additional efficacy analyses in the subgroups of patients previously treated and untreated in Study HGT-SAN-093 may be performed.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis. The data included for treated patients in HGT-SAN-093 starts from the baseline of Study HGT-SAN-093 and for patients who received no treatment in HGT-SAN-093 from the baseline of Study SHP-610-201. Baseline is the assessment obtained during the initial study period, prior to the first dose of HGT-1410, regardless of whether this occurred in Study HGT-SAN-093 or SHP-610-201.

Date of Original Protocol: 23 September 2014

Date of Amendment 1: 17 December 2015

Date of Amendment 2: 25 January 2017

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	antibody
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT; SGPT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST; SGOT	aspartate aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{0\text{-last}}$	area under the curve from the time of dosing to the last measurable concentration
$AUC_{0\text{-}\infty}$	area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration
BBB	blood-brain barrier
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CK	creatine kinase
$CL/_F$	total body clearance for extravascular administration divided by the fraction of dose absorbed
Cl	chloride
C_{max}	maximum concentration occurring at t_{max}
CNS	central nervous system
CO_2	carbon dioxide
con meds	concomitant medications
CRO	contract research organization
CS	clinically significant
CSF	cerebrospinal fluid
DMC	Data Monitoring Committee
DQ	developmental quotient
DS	dermatan sulfate
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FT	full-time

Abbreviation	Definition
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hct	hematocrit
HCUQ	Healthcare Utilization Questionnaire
Hgb	hemoglobin
HNS	heparan N-sulfatase
HS	heparan sulfate
ICH	International Conference on Harmonisation
IDDD	intrathecal drug delivery device
IFU	Instructions for Use
IRB	Institutional Review Board
IT	Intrathecal(ly)
ITQoL	Infant Toddler Quality of Life Questionnaire™
ITT	intent-to-treat
IV	intravenous(ly)
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactate dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPS IIIA	mucopolysaccharidosis type IIIA or Sanfilippo syndrome type A
MRI	magnetic resonance imaging
NA	sodium
NCS	not clinically significant
NW	not working
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetics
PT	part-time
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
RBC	red blood cell
rhHNS	recombinant human heparan N sulfatase

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SGSH	sulfoglucosamine sulfohydrolase
SI	Standard International
SOC	system organ class
$t_{1/2}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
UADE	unanticipated adverse device effect
US(A)	United States (of America)
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
$V_{z/F}$	volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WBC	white blood cell
WHO-DD	World Health Organization-Drug Dictionary
λ_Z	first order rate constant associated with the terminal (log-linear) portion of the curve

1 INTRODUCTION

Mucopolysaccharidosis type IIIA (MPS IIIA, also called Sanfilippo syndrome type A) is a rare, autosomal recessive, lysosomal storage disease (LSD) presenting in early childhood that causes progressive neurodegeneration associated with intractable behavioral problems and developmental regression. Ultimately, a vegetative state supervenes. Life span is shortened, with death usually occurring in the late teen years. The genetic defect in this disorder is a mutation in both copies of the sulfoglucosamine sulfohydrolase (SGSH) gene, located on chromosome 17, which encodes the lysosomal enzyme, sulfoglucosamine sulfohydrolase, also called heparan-N-sulfatase, or sulfamidase. This enzyme is necessary for the normal intralysosomal catabolism of the glycosaminoglycan (GAG) (formerly termed mucopolysaccharide), heparan sulfate (HS). Sulfoglucosamine sulfohydrolase deficiency therefore results in the accumulation of heparan sulfate in lysosomes. Although the metabolic defect is expressed in every organ, the clinical manifestations of disease are primarily neurological. These are not usually apparent until 1 to 4 years of age. The molecular events linking the primary metabolic defect to the consequent neuropathology are not understood.

MPS III is the most prevalent of the mucopolysaccharidoses and consists of 4 subtypes, A, B, C, and D.[1] Each of these is characterized by a deficiency of a distinct lysosomal enzyme necessary for the degradation of heparan sulfate. Clinically, on an individual patient level, the 4 subtypes cannot be reliably distinguished. Globally, subtype A is the most prevalent, at approximately 1 case in 100,000 live births, followed by subtype B, at approximately 1 in 250,000 live births.[1-3] Among MPS IIIA patients, there is wide allelic heterogeneity, with at least 100 SGSH mutations described to date. Most of these are missense, but nonsense mutations, deletions, insertions and splice-site mutations also occur.[4]

MPS IIIA symptoms usually arise in the first or second year of life, although diagnosis is delayed until an average age of 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors that include aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5-7] There are also reports of unexplained, recurrent and severe diarrhea.[6] Overall, individuals with MPS IIIA exhibit progressive dementia with ultimate inanition and death resulting from the CNS disease. Lifespan is severely curtailed, with usual survival into the late teens.[6] Milder variants are recognized, with slower progression and survival to later age. The latter has been reported in approximately 10% of German patients with MPS IIIA, in association with the presence of the S298P mutation.[8]

No effective, disease-modifying therapies are currently approved as treatments for this devastating and disabling disease. A goal of Shire is to develop recombinant human heparan-N-sulfatase (rhHNS, development name HGT-1410) as enzyme replacement therapy (ERT) for patients with MPS IIIA. A particular problem for lysosomal storage disorders that damage the brain, such as MPS III, is how to target ERT to the brain, as macromolecules cannot cross the blood-brain barrier (BBB).[9] In animal studies, ERT has been administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously

(IV) it does not cross the BBB after the immediate postnatal period of life. HGT-1410 has been shown to be ineffective if administered intravenously in the MPS IIIA mouse model, in contrast to its efficacy in treating CNS pathology when administered into the CSF.[10]

In order to traverse the BBB, HGT-1410 will be administered directly to the CNS using an IT drug delivery device (IDDD) or, if the IDDD is non-functional, via lumbar puncture (LP). The advantage of using an IDDD is the potential to obviate the need for multiple LPs for drug delivery. HGT-1410 will be administered through the IDDD or, if the IDDD is non-functional, via LP.

Please refer to the current edition of the Investigator's Brochure for further information concerning the nonclinical studies completed, including safety and clinical development of HGT-1410.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate long-term safety in patients with mucopolysaccharidosis type IIIA disease (MPS IIIA or Sanfilippo syndrome type A) who received HGT-1410.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- The long-term cognitive function as measured by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II), age-equivalent and developmental quotient (DQ) scores in patients with MPS IIIA who received HGT-1410
- The long-term adaptive behavioral function, assessed by Vineland Adaptive Behavior Scales, Second Edition (VABS-II) in patients who received HGT-1410
- The total cortical grey matter volume, as assessed by volumetric magnetic resonance imaging (MRI) of the brain, in patients who received HGT-1410

2.3 Exploratory Objective

The exploratory objective of this study is [redacted].

2.4 Pharmacokinetic and Pharmacodynamic Objectives

The pharmacokinetic and pharmacodynamics objectives of this study are to evaluate:

- The pharmacokinetics of HGT-1410 in serum
- The pharmacokinetics of HGT-1410 in CSF, in patients who received no treatment in Study HGT-SAN-093
- The concentration of GAG in CSF and urine in patients who received HGT-1410

2.5 Health Status Objective

The health status objective of this study is to evaluate health status as measured by the Infant Toddler Quality of Life Questionnaire™ (ITQoL) instrument in patients who received HGT-1410.

2.6 Health Economics and Outcome Research Objective

The health economics and outcome research objective of this study is to evaluate healthcare resource utilization, as evaluated by the Healthcare Utilization Questionnaire (HCUQ), in patients who received HGT-1410.

3 STUDY ENDPOINTS

3.1 Primary Endpoint

Safety is the primary objective of the study and will be assessed during the study by the following:

- Collection of adverse events (AEs; by type, severity, and relationship to treatment [HGT-1410, the IDDD, device surgical procedure, or IT administration process])
- Changes in clinical laboratory testing (serum chemistry, hematology, urinalysis)
- Physical examination
- Vital signs
- Twelve-lead electrocardiogram (ECG) recordings
- CSF laboratory parameters (including chemistries, cell counts)
- Anti-rhHNS antibodies in CSF and serum, including determination of antibodies having enzyme neutralizing activity

3.2 Secondary Endpoints

The secondary endpoints of this study are:

- The change from Baseline in BSID-III or KABC-II age-equivalent, DQ, and developmental delay scores
- The change from Baseline in adaptive behavioral function domains, assessed by VABS II, using raw scores, age-equivalent scores, and DQ scores
- The change from Baseline in total cortical grey matter volume, as assessed by MRI

3.3 Exploratory Endpoint(s)

[redacted]

3.4 Pharmacokinetic and Pharmacodynamic Endpoints

The pharmacokinetic endpoint is to determine the pharmacokinetic behavior of HGT-1410 in serum, based on the following parameters:

- Maximum concentration occurring at t_{max} (C_{max})
- Time of maximum observed concentration sampled during a dosing interval (t_{max})
- Area under the curve from the time of dosing to the last measurable concentration ($AUC_{0\text{-}last}$)
- Area under the curve extrapolated to infinity, calculated using the observed value of the last non-zero concentration ($AUC_{0\text{-}\infty}$)
- First order rate constant associated with the terminal (log-linear) portion of the curve (λ_Z)
- Terminal half-life ($t_{1/2}$) calculated as $0.693/\lambda_Z$

- total body clearance for extravascular administration divided by the fraction of dose absorbed ($CL/_F$)
- Volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed ($V_z/_F$)

The pharmacodynamic endpoint is to determine the GAG concentrations in CSF and urine.

3.5 Health Status Endpoint

The health status endpoint is the ITQoL scores at each assessment time and the corresponding change from Baseline.

3.6 Health Economics and Outcomes Research Endpoint

The health economic and outcome research endpoints evaluate the key HCUQ variables, such as the number of emergency room visits, caregiver employment status (full-time [FT], part-time [PT], and not working [NW]), and the number of hours of additional paid help needed by caregivers, over the course of the study.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label extension study of HGT-1410 for patients who completed through at least the Week 48 Visit in Study HGT-SAN-093. The study design is presented in Figure 1. Patients who originally received HGT-1410 in Study HGT-SAN-093 will remain on the same dosing regimen as they received in Study HGT-SAN-093; Group 1 will receive HGT-1410 Q2W and Group 2 will received HGT-1410 Q4W. Patients in Groups 1 and 2 will begin treatment at Week 50 and Week 52, respectively, of this extension study (Study SHP-610-201). Patients who originally received no-treatment in Study HGT-SAN-093 (Group 3) will receive an IDDD following informed consent and will be re-randomized in a 1:1 allocation ratio to receive HGT-1410 via a Q2W or Q4W dosing regimen (Groups 3A and 3B, respectively) in Study SHP-610-201. Patients in Groups 3A and 3B will begin treatment on Week 0 of the extension study.

The Sponsor and Principal Investigator will consider the feasibility of transitioning the patient's IT dosing to local sites to reduce the burden imposed by travel. The local sites will be selected and approved by the Sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: The main site may serve as a local site as needed, and in this case, the main site will follow the assessment schedule for a local site). The qualification requirements for physicians at local sites will be identical to those for the main sites. Local sites will be experienced with IT administration via an IDDD. For patients who were in the no-treatment group in the HGT-SAN-093 study, initial IT administrations will be at the main study site following IDDD implantation until in the opinion of the Principal Investigator there are no safety or medical concerns precluding the patient from transitioning. Patients will be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the Investigator. Exceptions include the IT injections of HGT-1410 when scheduled study assessments are scheduled; these will take place at the main site. Patients that have already received IT drug administration at the main study site would be eligible to transfer to a local site starting at Week 50 (Group 1) or Week 52 (Group 2) in SHP-610-201 if in the opinion of the Principal Investigator there are no safety or medical concerns precluding the patient from transitioning.

It is anticipated that the IDDD will be used to collect CSF samples and to deliver IT injections of HGT-1410 and preservative-free saline flushes. No other medication will be administered through the device. If the IDDD appears to be non-functional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD Manual, which provides details on the investigation and management of any IDDD-related issues. This includes possible partial revision or complete replacement of the IDDD as indicated. If the IT space is not accessible via the IDDD, study drug 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. General anesthesia or sedation may be required for injections of study drug and some evaluations, and may be used at the discretion of the Investigator. The Data Monitoring Committee (DMC) will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter (see Section 11.8).

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

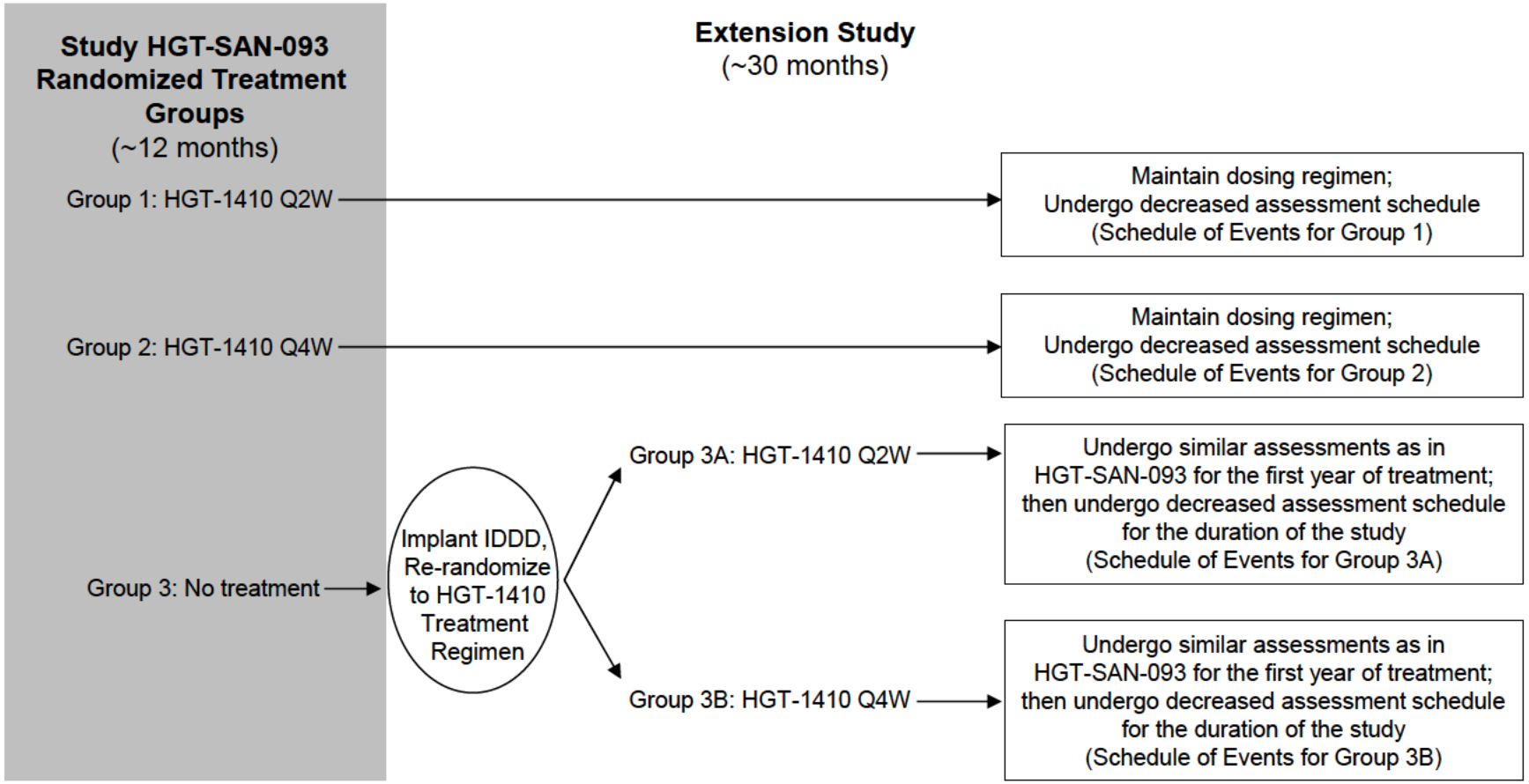
Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of the treatment period of the extension study. A pharmacokinetic sample for patients who received HGT-1410 in Study HGT-SAN-093 will be obtained at the Week 96 visit (after approximately 2 full years of exposure to HGT-1410 across Studies HGT-SAN-093 and SHP-610-201). Serum pharmacokinetic samples for patients who received no-treatment in Study HGT-SAN-093 will be obtained at the Week 0, 48, and 96, and CSF pharmacokinetic samples will be obtained on the Week 0 and 48 visits in Study SHP-610-201.

Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

Patients who do not have the IDDD removed (partial or full device) at the end of the treatment period will continue to be observed during a safety follow-up period with visits at the site every 6 months to evaluate patient safety of the device until the IDDD has been fully explanted.

See Appendix 1, Appendix 2, Appendix 3, and Appendix 4 for the Study Schedule of Events tables for Groups 1, 2, 3A, and 3B, respectively. See Appendix 5 for the Study Schedule of Events for the safety follow-up period for patients with partial or full devices in place after the end of the treatment period.

Figure 1 SHP-610-201 Study Design



Abbreviations: IDDD=intrathecal drug delivery device; Q2W=every 2 weeks; Q4W=every 4 weeks

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

The study design is intended to provide ongoing treatment with HGT-1410 to patients who received HGT-1410 in Study HGT-SAN-093 and to initiate treatment to patients who received no-treatment in Study HGT-SAN-093. As such, all patients will be treated during this study; there is no control group.

In order to traverse the blood-brain barrier, HGT-1410 will be administered directly to the CNS using an IDDD or, if the IDDD is non-functional, via LP. The advantage of using an IDDD is the potential to obviate the need for multiple lumbar punctures for drug delivery. HGT-1410 will be administered through the IDDD or, if the IDDD is non-functional, via lumbar puncture.

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

4.3 Study Duration

Patients who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201.

Patients with a partial or full device still in place after completion of the treatment period may be followed for safety up to an additional 3 years or until the device is removed in the last patient.

The LPLV will be the safety follow-up visit after the final device (partial and/or full) is removed from the last patient during the safety follow-up period.

5 STUDY POPULATION SELECTION

5.1 Study Population

A maximum of 21 patients with MPS IIIA who completed Study HGT-SAN-093 are planned to enroll in this study.

5.2 Inclusion Criteria

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

1. Patient has completed through at least the Week 48 visit of Study HGT-SAN-093.
2. The patient's parent(s) or legally authorized guardian(s) has voluntarily signed an Institutional Review Board (IRB)/ ethics committee (EC)–approved informed consent form after all relevant aspects of the study have been explained and discussed. Consent of the patient's parent(s) or legally authorized guardian(s) and the patient's assent, as relevant, must be obtained.

5.3 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria are met:

1. The patient, if randomized to treatment in Study HGT-SAN-093, has experienced a decline of more than 20 points in the BSID-III cognitive DQ score between Baseline and the Week 48 visit in Study HGT-SAN-093, AND, upon individual evaluation by the Investigator, has been deemed a treatment failure*.
2. The patient has experienced, in the opinion of the Investigator, a safety or medical issue that contraindicates treatment with HGT-1410, including but not limited to clinically relevant intracranial hypertension, severe infusion-related reactions after treatment with HGT-1410, uncontrollable seizure disorder.
3. The patient has a known hypersensitivity to any of the components of HGT-1410. Patients with documented infusion-related reactions that are clinically manageable (for example, with pre-medication or slowing infusion rate) are not necessarily excluded based on the assessment of the Investigator.
4. The patient is enrolled in another clinical study, other than HGT-SAN-093, that involves clinical investigations or use of any investigational product (drug or [intrathecal/spinal] device) within 30 days prior to study enrollment or at any time during the study.
5. The patient has any known or suspected hypersensitivity to anesthesia or is thought to be at an unacceptably high risk for anesthesia due to airway compromise or other conditions.
6. The patient has a condition that is contraindicated as described in the SOPH-A-PORT Mini S IDDD Instructions for Use (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's drug therapy requires substances known to be incompatible with the materials of construction.
d. The patient has a known or suspected local or general infection.
e. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
f. The patient has 1 or more spinal abnormalities that could complicate safe implantation or fixation.
g. The patient has a functioning CSF shunt device.
h. The patient has shown an intolerance to an implanted device.

7. The patient is unable to comply with the protocol (eg, is unable to return for safety evaluations or is otherwise unlikely to complete the study) as determined by the Investigator.

*All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in the BSID-III DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Investigational Product

The investigational product to be used in this study is HGT-1410, rhHNS for IT use.

The HGT-1410 drug product is a sterile solution for injection in single-use vials for IT administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, 0.02% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.

6.1.2 Intrathecal Drug Delivery Device

The drug product will be administered via the SOPH-A-PORT Mini S Implantable Access Port. The SOPH-A-PORT Mini S device is intended for long-term, intermittent access to the IT space for the delivery of investigational drug. The device is Conformité Européenne (CE)-marked in the European Union (EU) and investigational in non-EU countries.

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

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

Further details are provided in the SOPH-A-PORT Mini S IFU.

6.1.3 Comparator Product

Not applicable

6.2 Treatment Administered

The study drug will be administered through an IDDD. In the event of IDDD malfunction or failure, HGT-1410 may be administered via LP.

Patients who were randomized to receive HGT-1410 in Study HGT-SAN-093 will continue to have HGT-1410 administered through the IDDD that was implanted during Study HGT-SAN-093.

Patients who were randomized to no treatment in Study HGT-SAN-093 will be scheduled to undergo surgical placement of the SOPH-A-PORT Mini S device. The initial implantation and any revision and/or explantation of the SOPH-A-PORT Mini S will be performed by pediatric or general neurosurgeons or anesthesiologists who have experience in port and catheter implant procedures and IT-access procedures and have completed training for the SOPH-A-PORT Mini

S. Please refer to the IFU for further details. At least 7 days will be allowed for recovery following the placement of the IDDD before the administration of the first intrathecal dose of HGT-1410. During this time, the patient will receive standard perioperative care.

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

As previously noted, under the appropriate conditions, IT HGT-1410 may be administered at local sites rather than main sites to reduce the burden of monthly travel. This is further detailed in Section 4.1.

6.3 Selection and Timing of Dose for Each Patient

After meeting eligibility criteria, patients in Groups 1 and 2 (who received HGT-1410 in Study HGT-SAN-093) will begin treatment at Weeks 50 and 52, respectively, in Study SHP-610-201. Patients will be treated for up to 120 weeks in Study SHP-610-201, for a total cumulative exposure of 168 weeks across Studies HGT-SAN-093 and SHP-610-201.

After meeting eligibility criteria, patients who were randomized to no treatment in Study HGT-SAN-093 will be scheduled to undergo surgical placement of the SOPH-A-PORT Mini S device, as described in Section 6.2. Thereafter, these patients will be administered HGT-1410 45 mg as an IT injection either Q2W or Q4W (Groups 3A or 3B, respectively), as randomized, for up to 120 weeks.

6.3.1 Missed Doses

Patients who are scheduled to receive Q2W dosing (Groups 1 and 3A) should receive their dose of HGT-1410 every 14±3 days, and patients who are scheduled to receive Q4W dosing (Groups 2 and 3B) should receive their dose of HGT-1410 every 28±7 days. If dosing cannot be administered within the indicated time window, the dose will be considered missed, and the patient will resume their dosing schedule with the next dose of HGT-1410. The dosing schedule will not change or be reset.

6.4 Method of Assigning Patients to Treatment Groups

Patients who were randomized to no-treatment in Study HGT-SAN-093 (Group 3) will be re-randomized in a 1:1 allocation ratio to receive Q2W or Q4W dosing (Groups 3A or 3B, respectively). To help ensure balance between the dose groups with respect to age at Baseline, the randomization will be stratified by age group (≤30 months and >30 months; see Section 10.3).

Patients who were randomized to receive HGT-1410 in Study HGT-SAN-093 will remain on the same treatment regimen in Study SHP-610-201.

6.5 Blinding

This study will not be blinded.

6.6 Prior and Concomitant Medications, Therapies, and Medical/Surgical Interventions

Prior and/or concomitant therapy prohibited for all patients in this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results
- The use of medications which, in the opinion of the Investigator, would place patients at risk of bleeding complications following surgery or LP
- Any other investigational therapy (drug or device) at any time during the study
- Hematopoietic stem cell or bone marrow transplant

6.7 Restrictions

6.7.1 Fluid and Food Intake

Not applicable

6.7.2 Patient Activity Restrictions

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

6.8 Treatment Compliance

Treatment with HGT-1410 will be administered via an IDDD under the supervision of the investigator and in the controlled environment of a clinical center; therefore, full patient compliance with treatment is anticipated in this study.

6.9 Packaging and Labeling

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

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 and will be in accordance with local regulatory requirements.

6.10 Storage and Accountability

6.10.1 Investigational Product

HGT-1410 will be supplied at a concentration of 15 mg/mL in single-use vials for IT administration.

HGT-1410 will be shipped by Shire or a qualified distributor to the clinical study site(s) at 2 to 8°C (36-46°F).

Drug product should be stored refrigerated (2-8°C); drug product may not be used beyond the expiration date on the vial.

The disposition of all investigational product delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the clinical trial material accountability log. The date and time of administration of the investigational 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 product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

The process for destruction of investigational product is provided in the Pharmacy Manual.

See the Pharmacy Manual for additional details.

6.10.2 Intrathecal Drug Delivery Device

The disposition of all SOPH-A-PORT Mini S devices delivered to a Principal Investigator must be recorded on a patient-by-patient basis by completing the Accountability Log. The date and time of administration of the investigational product and use of the SOPH-A-PORT Mini S device must be documented on the 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 devices and return of used/unused SOPH-A-PORT Mini S device(s) is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the SOPH-A-PORT Mini S devices are available for the monitor to inventory and prepare for product destruction or return shipment to the Sponsor or designee.

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

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

6.10.3 Comparator Product

Not applicable to this study.

7 STUDY PROCEDURES

Detailed descriptions of patient procedures and evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see Schedule of Events for Group 1 [patients who received HGT-1410 Q2W in Study HGT-SAN-093[in Appendix 1, for Group 2 [patients who received HGT-1410 Q4W in Study HGT-SAN-093] in Appendix 2, for Group 3A [patients who received no treatment in Study HGT-SAN-093 and are randomized to receive HGT-1410 Q2W in Study SHP-610-201] in Appendix 3, and for Group 3B [patients who received no treatment in Study HGT-SAN-093 and are randomized to receive HGT-1410 Q4W in Study SHP-610-201] in Appendix 4).

See Appendix 5 for the Study Schedule of Events for the safety follow-up period for patients with partial or full devices in place after the end of the treatment period.

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

Details for sample collection are described in the Laboratory Manual for Study SHP-610-201.

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).

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 and filing of informed consent documents should be completed according to Section 11.4.

After the treatment period ends, informed consent from patients who do not have the IDDD removed (partial or full device) will be obtained for the safety follow-up period.

7.2 Study Entrance Criteria

Each patient in Groups 1 and 2 (those who received HGT-1410 in Study HGT-SAN-093) will be reviewed for eligibility against the study entrance criteria prior to receiving HGT-1410 at Weeks 50 and 52, respectively.

All treated patients in Study HGT-SAN-093 will have their cognitive development assessed at the Week 48 Visit in Study HGT-SAN-093. If a decline from Baseline of 20 points or less in DQ score is observed, then the patient may proceed into the Study SHP-610-201 without further evaluation. If a decline from Baseline of more than 20 points in DQ score is observed, then an individual evaluation by the Investigator will occur to determine if the patient is a treatment failure. This individual evaluation will take into account the DQ scores, VABS-II score, physical status, and any other information available for that patient at that time. If the Investigator deems the patient to be a treatment failure, then the patient may not enter the Study SHP-610-201.

Each patient who received no treatment in Study HGT-SAN-093 (Group 3) will be reviewed for eligibility against the study entrance criteria before IDDD implantation.

Patients who do not 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.

7.3 Hearing and Vision Assessments

7.3.1 Investigator Assessment of Hearing and Vision

For patients who received no-treatment in Study HGT-SAN-093 (Group 3) only, the Investigator will use their clinical judgment to assess the patient's vision during the initial physical examination. Investigator judgment will be used to determine whether the patient's hearing and vision is adequate for cooperation with neurodevelopmental testing, as indicated in the study inclusion criteria.

7.4 Device-related Study Procedures

7.4.1 IDDD Implantation or Revision Procedures

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

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

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

7.4.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative X-ray check of the IDDD will be performed following surgery for Groups 3A and 3B to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The X-rays may be performed to check placement, migration, or malfunction of the device, as needed, throughout the treatment period or safety follow-up period of the study. At a minimum, the date of the X-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the treatment period of the study, additional X-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray will be performed to assess the potential cause of malfunction. Fluoroscopy should be used during device implantation procedures.

7.4.3 CSF Sampling Procedure

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

7.4.4 Device Adjustment, Revision, or Removal

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

The IDDD will then be surgically adjusted, 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.

Details of the device removal will be recorded in the patient's eCRF. Refer to the SOPH-A-PORT Mini S IFU for further details.

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

7.5 Investigational Product Administration

Patients will be administered HGT-1410 by means of an IDDD, either every 2 weeks (Q2W) or every 4 weeks (Q4W). 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 4 hours post-dosing and will be discharged when deemed clinically stable by the Investigator. The number of IDDD revisions/replacements is limited to 2 per patient in any 6-month period. Therefore, in the "worst case scenario" of 2 IDDD failures occurring within 1 month, up to 11 consecutive doses of HGT-1410 administered via LP will be necessary for patients in the Q2W dosing group, and up to 5 consecutive doses via LP will be necessary for patients in the Q4W dosing group until the IDDD can be revised or replaced.

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

It is expected that all or most doses of HGT-1410 will be successfully administered following the application of topical anesthetic cream to the skin overlying the IDDD access port (see IDDD Manual for details). However, in some cases, sedation or general anesthesia may be required and may be used at the discretion of the Investigator. Any sedative or anesthetic drugs used must be recorded as concomitant medications.

Intrathecal administration of investigational product will be preceded by CSF sampling for clinical laboratory analysis (cell count, protein, glucose) and storage for additional analyses which may include pharmacodynamics (GAG concentration) and analyses of HGT-1410 enzyme and anti-rhHNS antibodies, according to the relevant Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

All HGT-1410 administrations will be followed by a flush with preservative-free saline of at least 2 mL. The total volume of investigational product and flush administered is targeted towards replenishing the volume of CSF withdrawn. If the total volume of HGT-1410 plus 2 mL saline flush is less than the total volume of CSF withdrawn, additional saline will be administered to balance the volumes withdrawn and injected.

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

7.6 Efficacy Assessments

7.6.1 Neurocognitive and Developmental Assessments

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of patient neurodevelopmental status (see Table 7-1).[11] The assessments are estimated to last between 2 and 4 hours and must be conducted prior to any invasive procedures, such as blood draws, and prior to sedation or anesthesia. Neurodevelopmental status will be assessed over time by measuring cognitive and adaptive functions as follows:

- Cognition: The BSID-III[12] will be used to assess all patients through the age of 42 months. Once patients reach age 42 months, an attempt will be made to switch the cognitive assessment to the KABC-II. If the cognitive status of the patient does not allow for testing by the KABC-II, the BSID-III may be used.
- Adaptive behaviors: The VABS-II[13] will be used to assess all patients.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments are summarized below in Table 7-1.

Table 7-1 Neurodevelopmental Assessments Tests

Cognitive Test or Scale	Developmental or Cognitive Areas of Assessment
BSID-III[12]	Summary score and sub-domains: - Cognitive - Motor - Social/Emotional - Language
KABC-II	Cognitive and processing skills
ADAPTIVE BEHAVIOR	
VABS-II[13]	Communication Daily Living Socialization Motor Skills

Abbreviations: BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; KABC-II=

Table 7-1 Neurodevelopmental Assessments Tests

Cognitive Test or Scale	Developmental or Cognitive Areas of Assessment

Kaufman Assessment Battery for Children, Second Edition; VABS-II=Vineland Adaptive Behavior Scales, Second Edition

7.6.2 Quality of Life Indicator: Infant Toddler Quality of Life Questionnaire

The ITQoL will be administered during the study. The ITQoL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well-being of the child and assesses the quality of the parent/guardian's life. If a patient is over 5 years of age, they do not have to complete the ITQoL.

7.6.3 Health Economics and Outcomes Research: Healthcare Utilization Questionnaire

The HCUQ will be administered during the study. This HCUQ focuses on the direct and indirect costs of care for patients with MPS-III.

7.7 Magnetic Resonance Imaging

7.7.1 Head

Regional brain volumes, including total cortical gray matter volume, will be assessed through an MRI of the head. The patient will be under general anesthesia for this assessment. Instrument standardization and central analysis of MRIs will be performed by a designated contract research laboratory.

7.7.2 Liver and Spleen

Liver and spleen volumes will be assessed through an MRI, performed at the same times as for the MRI of the head. The patient will be under general anesthesia for this assessment. Instrument standardization and central analysis of MRIs will be performed by a designated contract research laboratory.

7.8 Pharmacokinetic Assessments

Blood samples will be collected for measurement of serum concentrations of HGT-1410 and determination of pharmacokinetic parameters at the times specified in the Schedules of Events (see Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 7). Additionally, CSF samples will be collected from patients who received no treatment in Study HGT-SAN-093 at the times specified in the Schedules of Events (see Appendix 3, Appendix 4, and Appendix 7). The results of these assessments will be addressed in a separate pharmacokinetics report.

Patients may be discharged from the hospital after the 24-hour blood draw. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); this will be decided in consultation with the Investigator. Patients will return to the hospital for pharmacokinetic blood and CSF sampling at the 48-hour time point. Patients will be discharged to home after the physical examination and blood draws have been completed at the 48-hour PK

time point. See Appendix 7 for more details regarding timing for pharmacokinetic sample collection.

Serum and CSF pharmacokinetic collection, processing, and shipping instructions will be provided in the Laboratory Operations Manual.

7.9 Pharmacodynamic Biomarker Assessments (CSF and Urine GAG Levels)

CSF and urine samples will be obtained to measure the concentration of GAG according to the schedules of events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4). Details about CSF collection are provided in Section 7.11.5.3.

7.10 Concomitant Medications, Therapies, and Medical/Surgical Interventions

All non-protocol treatments and medications that occur from the time of informed consent through the safety follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the eCRF. Concomitant therapy includes any therapies/interventions administered to patients, and these will be recorded on the concomitant therapy eCRF. Any medical/surgical procedures performed on the patients will be recorded on the concomitant medical/surgical procedures eCRF. Concomitant medications, both prescribed and over-the-counter (including genistein and anesthesia medications) will be recorded on the concomitant medication eCRF.

Every effort should be made to keep symptomatic MPS IIIA treatment constant throughout the study. However, changes in medications are acceptable if necessary according to clinical judgment. All changes will be recorded on the appropriate eCRF. Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

7.11 Safety Assessments

7.11.1 Vital Signs

Vital signs are to be recorded on the eCRF for all patients and will include heart rate, blood pressure, respiration rate, and body temperature. Vital signs will be recorded for at least 4 hours following each dose of HGT-1410, as described in the Schedules of Events (Appendix 1, Appendix 2, Appendix 3, and Appendix 4).

7.11.2 Physical Examination, Including Height, Weight, and Head Circumference

During the study, physical examinations will be performed at the time points indicated in the Schedules of Events. For Groups 1 and 2, full physical examinations will be conducted at Weeks 96, 120, 144, and 168, and for Groups 3A and 3B, full physical examinations will be conducted during the IDDD implantation period and at Weeks 24, 48, 72, 96, and 120. The remainder of physical examinations will be symptom-directed, including examinations during the safety follow-up period in patients who do not have the IDDD removed (partial or full device) at the end of the treatment period.

Physical examinations will include a review of the patient's general appearance, neurological examination, as well as evaluation of the body systems described in Table 7-2, including the port

and catheter track. Any abnormal change in findings will be recorded as an AE on the appropriate eCRF.

Table 7-2 Assessments for Physical Examinations

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

Height and weight will be recorded for all patients.

The clinical site staff will be instructed to use calibrated scales for weight measurement where possible. The same scale is to be used at the clinical site for all patients at each specified time point during the study.

Head circumference will be measured for Groups 3A and 3B during the IDDD implantation period. All data will be recorded on the eCRF.

7.11.3 Electrocardiogram

An ECG will be performed in accordance with the clinical site's standard practice(s) and are to be performed after study drug administration. Electrocardiogram recordings will be read locally at the clinical site and will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, and QT. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF. If the patient is unable to cooperate with electrocardiography, and if sedation or general anesthesia is employed during that study visit, the ECG may be performed under sedation/anesthesia.

7.11.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected via venipuncture. Patients will be in a seated or supine position during blood collection. Procedures for collection and handling of samples are included in the Laboratory Manual. Blood volumes are presented in Appendix 6.

Clinical laboratory testing will only be performed when indicated for a device-related AE for patients who do not have the IDDD removed (partial or full device) at the end of the treatment period.

Clinical laboratory tests will include the following (see Table 7-3):

Table 7-3 List of Laboratory Tests

Hematology:

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

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Microscopic examination
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen
- Triglycerides
- Uric acid

Anti-rhHNS antibody assessment

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Creatine kinase (CK) and subtypes
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Coagulation (performed at IDDD implantation):

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

7.11.5 Cerebrospinal Fluid Assessments

Cerebrospinal fluid will be obtained from patients during surgical implantation of the IDDD (Groups 3A and 3B only), immediately prior to each injection of study drug and at the safety follow-up visit. Should the IDDD become clogged or undergo mechanical complications, the CSF sample will be obtained via LP.

The volume of CSF collected at each visit will vary according to the number of CSF assessments. The initial 1 mL of CSF aspirated via the IDDD will be discarded, to eliminate fluid in the device's "dead space." The next 1 mL of CSF will be sent to the local laboratory. Subsequently drawn CSF will be stored, depending on the requirement for that visit (see the Schedules of Events in Appendix 1, Appendix 2, Appendix 3, Appendix 4, and the Laboratory Manual). If CSF is obtained via LP, there is no need to discard the first mL of CSF, and this can be sent to the local laboratory for standard clinical assessments. If the patient is clinically stable

in the opinion of the Investigator, HGT-1410 can be administered immediately following withdrawal of CSF, without awaiting the results of the CSF clinical laboratory data.

Each CSF sample collected will have the assessments described in Sections 7.11.5.1 through 7.11.5.4. Cerebrospinal fluid sample collection, processing, and shipping instructions are provided in the Laboratory Manual. Total CSF volumes are presented in Appendix 6.

7.11.5.1 Standard CSF Safety Laboratory Assessments

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

7.11.5.2 Anti-rhHNS Antibodies and Biomarkers in CSF

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of anti-rhHNS antibody evaluation, exploratory proteomics biomarkers, and/or other CSF biomarkers.

7.11.5.3 CSF GAG Levels and Biomarkers

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of CSF GAG, GAG degradation components, HS/dermatan sulfate (DS) oligosaccharides, or other CSF markers. The CSF pharmacodynamic sample will be obtained at the same visit as a serum sample as described in Section 7.9.

7.11.5.4 [redacted]

[redacted]

7.11.6 Device Assessments

[redacted] These data will be collected on the patient's eCRF from the time of initial implantation.

7.11.7 Collection and Storage of Biological Samples for Biomarker Studies

Biomarker analyses may be performed at the Shire research laboratory or at a Shire-designated research laboratory. Collection and processing of CSF samples will be performed as specified in the Laboratory Manual. Samples will be stored securely to ensure patient confidentiality. Samples obtained for this study will be stored for up to 10 years. Thereafter, samples will be destroyed.

7.12 Sample Collection, Storage, and Shipping

Details for study procedures including sample collection are provided in the Laboratory Manual for this study.

7.13 Adverse Events Assessments

7.13.1 Definitions of Adverse Events and Serious Adverse Events

7.13.1.1 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 product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- 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 eCRF, regardless of the severity or relationship to investigational product. 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.

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.

7.13.1.2 Adverse Events Due to Systemic Exposure to HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration. Investigators will judge the relationship of AEs to the drug infusion and describe the clinical details on the AE form. The temporal relationship of an AE to the drug infusion will be determined upon analysis of the AE and study treatment administration data.

7.13.1.3 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, 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

7.13.1.4 IDDD-related Adverse Events

IDDD 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 7.13.2.2) should not be entered as an adverse event unless it has physiological consequences. In the event of a device failure (defined in Section 7.13.2.3), the device may need to be replaced or repaired. If overnight hospitalization is required for such a procedure (or the device failure meets any other serious criteria, eg, medically important), the device failure will be reported as a serious adverse event. Details of the cause of the IDDD malfunction or failure will be recorded on the device malfunction and failure eCRF and the serious adverse event (SAE) form (when applicable). A list of the most common IDDD AEs is included in Appendix 8.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS (FOR IT STUDIES; AMEND/DELETE SECTION AS APPLICABLE)

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 postoperative complications (such as postoperative infection). These events are related to the surgical procedure itself.

IT ADMINISTRATION PROCESS ADVERSE EVENTS

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

7.13.1.5 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered 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).

An unanticipated adverse device effect (UADE) is any SAE 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).

7.13.2 Device-associated Definitions

7.13.2.1 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.

Device adjustment: surgery that does not result in partial or full device revision (see definition above) or removal. Examples of device adjustment include surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair.

7.13.2.2 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.

7.13.2.3 Device Failure

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

7.13.3 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the Investigator based on the definition indicated in Table 7-4. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page to a severity of mild, moderate, or severe.

Table 7-4 Adverse Event Severity

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

7.13.4 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.

7.13.5 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product, device (IDDD), device surgical procedure, or IT administration process will be assessed by the Investigator based on the following definitions (see Table 7-5).

Table 7-5 Adverse Event Relatedness

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

Table 7-5 Adverse Event Relatedness

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

7.13.6 Procedures for Recording and Reporting Adverse Events

7.13.6.1 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, the patient's parent(s), or the patient's legally authorized representative gives informed consent until the patient's final evaluation of the study. For safety purposes, the final evaluation for the treatment period will be defined as the follow-up evaluation performed approximately 30 days after the last dose for patients who complete the study. The final evaluation in the safety follow-up period for patients who do not have the IDDD removed (full or partial device) is defined as the follow-up evaluation performed for up to 3 years after the treatment period ends.

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.

7.13.6.2 Reporting Serious Adverse Events

Any SAE, regardless of relationship to investigational 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 product and/or device. 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:

Shire Pharmacovigilance and Risk Management Department:

International FAX: [redacted] **(UK) OR United States FAX:** [redacted]

Email: [redacted]

AND

Shire Medical Monitor: [redacted]**, DO**

Email: [redacted]

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

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

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

The Investigator must promptly report all required information to the IRB/EC. It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any Council for International Organizations of Medical Sciences I/MedWatch 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/EC receives a copy of the report and that a copy is also filed within their study files.

7.14 Abuse, Overdose and Medication Error

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

Misuse – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: 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 medicinal product higher than the protocol-mandated dose. No clinical information on overdose is available.

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

All investigational medicinal product provided to pediatrics should be supervised by the parent/legally authorized representative/caregiver.

7.15 Removal of Patients from the Trial or Investigational 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 one or more study visits
- The patient was erroneously included in the study.

- The patient develops an exclusion criterion.
- The patient suffers an intolerable AE.
- The study is terminated by the Sponsor.

The patient, the patient's parent(s), or the patient's legally authorized representative 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 or the patient's parent(s) or the patient's legally authorized representative(s) acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the safety follow-up assessments. The reason for refusal will be documented on the eCRF. Any AEs experienced up to the point of discontinuation must be documented on the AE eCRF. 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.

7.15.1 Study Discontinuation Process

If the patient is discontinued from the study, the IDDD should be removed and a modified end-of-study visit should be completed within 30 days after withdrawal. These visits may be combined into 1 visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. The end–of-study visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution.

If the investigator determines that the IDDD should not be removed from the patient based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit. This last treatment period visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution. Once the patient completes their last treatment period visit, they will return for their first safety follow-up visit in 6 months. The patient will continue in the safety follow-up period with a clinic visit every 6 months for up to 3 years or until the device is removed in the last patient. An end-of-study follow-up via a phone call should be completed within 14 days after the device removal to collect safety information (refer Section 8.6; Appendix 5).

7.16 Safety-Related Study Stopping Rules

In addition to safety monitoring by the Sponsor, patient safety in this study will be monitored by an independent DMC until the last patient completes their last scheduled study visit/assessment during the treatment period. The DMC will be an external group overseeing the safety of the

study treatment, including both the investigational product and the IDDD, and will operate according to a charter determining the scope of its activities and frequency of meetings (see Section 11.8 for additional details).

This study will be stopped and safety data reviewed if any patient experiences a life-threatening or fatal SAE, either of which is considered possibly or probably related to the investigational product.

Following the review of safety data, the status of the study will be one of the following:

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

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

7.17 Appropriateness of Measurements

The neurocognitive and developmental assessments planned for this study are intended to gauge the potential treatment effect and safety of 2 dose levels of HGT-1410 over time on behavioral and cognitive criteria in patients with MPS IIIA. The selection of tests used for the cognitive assessment, and the expression of results as a ratio of mental age equivalence to calendar age to generate a DQ, were developed in collaboration with clinical psychologists with expertise in the assessment of severely disabled children with neurometabolic diseases.

The BSID-III, KABC-II, and VABS-II are instruments that have been used to assess development in healthy children and those with developmental delay. Their use in this study will contribute to their validation in patients with MPS IIIA. The utility of these measures to track disease progression has been demonstrated in Shire's natural history study of MPS IIIA (HGT-SAN-053).

The BSID-III was selected for the following reasons:

- Widespread familiarity with the instrument
- Availability of age equivalent scores for severely impaired children
- Nonverbal content (ie, on the cognitive scale on the BSID-III)
- Availability of language and motor assessment (Both are domains on the BSID-III.)

The BSID-III is validated for children through the age of 42 months. Patients are to be switched to another instrument, the KABC-II, to measure cognition after the age of 42 months. The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

The VABS-II, a parent-reported outcome, was selected as an adaptive measure for the same reasons. Of note, to maximize standardization and reduce bias, the "interview" form of the VABS-II will be administered by the clinical psychologist/psychometrist at the same time as the BSID-III assessment.

The use of age equivalent scores rather than standard scores permits the assessment of children with severe disability in whom standard scores would otherwise be insensitive to change. Given the potentially rapid progression of MPS IIIA, a child who is assessable using a standard score at baseline may rapidly decline to such an extent that the assessment "floor" is reached and further change is not measurable. Additionally, the use of age equivalence scores permits comparison and correlation between the BSID-III and VABS-II. The use of DQ yields a parameter that tracks the dynamic progression of MPS IIIA disease, as observed in Shire's natural history study.

This study will utilize standard safety assessments including AEs, vital signs, standard clinical tests, and ECGs. Antibodies against the investigational drug will also be measured.

8 STUDY ACTIVITIES

The timing of study activities are described for each of the 3 patient groups below, and in Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively for Group 1 (initially randomized to receive HGT-1410 Q2W in Study HGT-SAN-093), Group 2 (initially randomized to receive HGT 1410 Q4W in Study HGT-SAN-093), Group 3A (initially randomized to no-treatment in Study HGT-SAN-093 and randomized to HGT-1410 Q2W in Study SHP-610-201), and Group 3B (initially randomized to no-treatment in Study HGT-SAN-093 and randomized to HGT-1410 Q4W in Study SHP-610-201). See Appendix 5 for the timing of study activities for the safety follow-up period for patients with partial or full devices in place after the end of the treatment period. Study activities for all patients are detailed in Section 7.

8.1 Group 1 (Maintaining Q2W Dosing)

8.1.1 Treatment Period (Weeks 50 through 168)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 1 will receive 45 mg HGT-1410 IT Q2W (ie, every 14±3 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

The first 48 weeks of treatment for Group 1 occurred in Study HGT-SAN-093, and therefore patients in Group 1 will begin this study at Week 50.

For patients in Group 1, HGT-1410 will be administered every other week from Week 50 through Week 168.

8.1.1.1 Pre-treatment Assessments

- Review of study eligibility and informed consent
- Full physical examination (PE), including height and weight at Weeks 72, 96, 120, 144, and 168; symptom-directed PE at all other visits
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 72, 96, 120, 144, and 168
- Quality of life (QoL) questionnaire: ITQoL for patients ≤5 years of age: Weeks 72, 96, 120, 144, and 168
- Health economics questionnaire: HCUQ: Weeks 72, 96, 120, 144, and 168
- MRIs of head, liver, and spleen: Weeks 96 and 144
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit before dosing: standard CSF safety laboratory assessments

- CSF and urine sample collection for GAG at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Serum pharmacokinetics sampling at Week 96 (see Appendix 7 for the pharmacokinetics collection schedule)

8.1.1.2 Post-treatment Assessments

- ECG at Weeks 96, 144, and 168
- Serum pharmacokinetics sampling at Week 96 (see Appendix 7 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment (unless the Investigator determines that the device should not be removed for safety reasons)

8.1.2 Safety Follow-up Visit: Week 172 (±7 days)

All patients will have a safety follow-up visit at Week 172 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.2 Group 2 (Maintaining Q4W Dosing)

8.2.1 Treatment Period (Weeks 52 through 168)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 2 will receive 45 mg HGT-1410 IT Q4W (ie, every 28±7 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

The first 48 weeks of treatment for Group 2 occurred in Study HGT-SAN-093, and therefore patients in Group 2 will begin this study at Week 52.

For patients in Group 2, HGT-1410-IT Q4W study drug will be administered Q4W from Week 52 through Week 168.

8.2.1.1 Pre-treatment Assessments

- Review of study eligibility and informed consent
- Full PE, including height and weight at Weeks 72, 96, 120, 144, and 168; symptom-directed PE at all other visits
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 72, 96, 120, 144, and 168
- QoL questionnaire: ITQoL for patients ≤5 years of age: Weeks 72, 96, 120, 144, and 168
- Health economics questionnaire: HCUQ: Weeks 72, 96, 120, 144, and 168
- MRIs of head, liver, and spleen: Weeks, 96 and 144
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168
- Serum PK sampling at Week 96 (see Appendix 7 for the pharmacokinetics collection schedule)_

8.2.1.2 Post-treatment Assessments

- ECG at Weeks 96, 144, and 168
- Serum PK sampling at Week 96 (see Appendix 7 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment (unless the Investigator determines that the device should not be removed for safety reasons, please see Section 8.6)

8.2.2 Safety Follow-up Visit: Week 172 (±7 days)

All patients will have a safety follow-up visit at Week 172 or 30 (±7) days after their last dose of HGT-1410:

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.3 Group 3 (Patients Randomized to No Treatment in Study HGT-SAN-093)

Patients in Group 3 received no treatment in Study HGT-SAN-093, and therefore these patients will begin this study at Day -27 to -7.

8.3.1 IDDD Implantation (Days -21 to Day -7)

8.3.1.1 Prior to IDDD Implantation

Prior to enrollment in the study, patients who were initially randomized to no treatment in Study HGT-SAN-093 will undergo the following assessments during the IDDD implantation period, prior to IDDD implantation surgery:

• Written informed consent • Assessment of eligibility according to inclusion/exclusion criteria • Vital signs • Investigator assessment of vision and hearing ability • PE, including height, weight, and head circumference • ECG	• Clinical laboratory tests, including PT and aPTT • BSID-III/KABC-II • VABS-II • ITQoL (for patients ≤5 years of age) • HCUQ • Concomitant medications, therapies, and procedures • AE monitoring

The PE, ECG, height, weight, and clinical labs (hematology, serum chemistry, and urinalysis) need to be performed within 7 days prior to the IDDD implantation surgery date. If more than 7 days elapse between the date of these assessments and the IDDD implantation surgery date, the assessments must be repeated within 7 days prior to surgery.

8.3.1.2 Day of IDDD Implantation

Surgical implantation of the IDDD includes surgical implantation of the IDDD and a post-surgical assessment. IDDD placement will require anesthesia.

Assessments to be performed on the day of IDDD implantation include:

Prior to anesthesia:	During time patient is anesthetized:
• Symptom-directed PE • ECG (before anesthesia if possible) • Vital signs • AE monitoring • Concomitant medications, therapies, and procedures	• If logistically possible, head, liver, and spleen MRI (before IDDD implantation) • IDDD implantation • CSF samples collected for clinical laboratory analysis (chemistry, cell count), CSF GAG, CSF storage for biomarkers • Postoperative: X-ray to check IDDD placement

8.3.2 Postoperative Check – Days 1 to 3

The postoperative check can occur anytime 1 to 3 days after IDDD implantation. Assessments include postoperative check of the IDDD incision; vital signs; symptom-directed PE; concomitant medications, therapies, and procedures; and AE monitoring.

8.3.3 Randomization (Can Occur Any Time After Meeting Study Entry Criteria)

All patients in Group 3 (patients who were initially randomized to no treatment in Study HGT-SAN-093) will be randomized in a 1:1 allocation ratio to receive Q2W or Q4W dosing (Groups 3A or 3B, respectively), as described in Section 6.4.

8.4 Group 3A (Initiating HGT-1410 Q2W Dosing)

8.4.1 Treatment Period (Weeks 0 through 120)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 3A will receive 45 mg HGT-1410 IT Q2W (ie, every 14±3 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

For patients in Group 3A, HGT-1410 will be administered every other week from Week 0 through Week 120.

8.4.1.1 Pre-treatment Assessments

- Full PE, including height and weight at Weeks 24, 48, 72, 96, and 120; symptom-directed PE at all other visits.
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring
- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 24, 48, 72, 96, and 120
- QoL questionnaire: ITQoL for patients ≤5 years of age: Weeks 24, 48, 72, 96, and 120
- Health economics questionnaire: HCUQ: Weeks 24, 48, 72, 96, and 120
- MRIs of head, liver, and spleen: Weeks 24, 48, and 96
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, and 120
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 7 for the pharmacokinetics collection schedule)

- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 7 for the pharmacokinetics collection schedule)

8.4.1.2 Post-treatment Assessments

- ECG at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 96, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 7 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 7 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment (unless the Investigator determines that the device should not be removed for safety reasons, please see Section 8.6)

8.4.2 Safety Follow-up Visit: Week 124 (±7 days)

All patients will have a safety follow-up visit at Week 24 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.5 Group 3B (Initiating HGT-1410 Q4W Dosing)

8.5.1 Treatment Period (Weeks 0 through 120)

The pre-treatment assessments may be performed on the same day as the administration of study drug if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

Patients in Group 3B will receive 45 mg HGT-1410 IT Q4W (ie, every 28±7 days). Administration of HGT-1410 can only occur following the completion of all pre-treatment assessments and procedures.

For patients in Group 3B, HGT-1410 will be administered Q4W from Week 0 through Week 120.

8.5.1.1 Pre-treatment Assessments

- Full PE, including height and weight at Weeks 24, 48, 72, 96, and 120; symptom-directed PE at all other visits
- Every visit: vital signs, concomitant medications, therapies, and procedures, and AE monitoring

- Cognitive/behavioral assessments: BSID-III/KABS-II and VABS-II: Weeks 24, 48, 72, 96, and 120
- QoL questionnaire: ITQoL for patients ≤5 years of age: Weeks 24, 48, 72, 96, and 120
- Health economics questionnaire: HCUQ: Weeks 24, 48, 72, 96, and 120
- MRIs of head, liver, and spleen: Weeks 24, 48, and 96
- Clinical laboratory tests: hematology, serum chemistry, urinalysis: Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Every study visit before dosing: standard CSF safety laboratory assessments
- CSF and urine sample collection for GAG at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, and 120
- Every study visit: CSF sample collection for storage for biomarkers
- Anti-rhHNS antibody testing (serum and CSF) and CSF biomarker testing at Weeks 0, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 7 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 7 for the pharmacokinetics collection schedule)

8.5.1.2 Post-treatment Assessments

- ECG at Weeks 0, 4, 8, 12, 16, 20, 24, 48, 96, and 120
- Serum pharmacokinetics sampling at Weeks 0, 48, and 96 (see Appendix 7 for the pharmacokinetics collection schedule)
- CSF pharmacokinetics sampling at Weeks 0 and 48 (see Appendix 7 for the pharmacokinetics collection schedule)
- Concomitant medications, therapies, and procedures
- AE monitoring
- Removal of IDDD if patient not continuing treatment (unless the Investigator determines that the device should not be removed for safety reasons, please see Section 8.6)

8.5.2 Safety Follow-up Visit: Week 124 (±7 days)

All patients will have a safety follow-up visit at Week 24 or 30 (±7) days after their last dose of HGT-1410.

- Symptom-directed PE
- Vital signs
- Clinical laboratory tests
- Concomitant medications, therapies, and procedures
- AE monitoring

8.6 All Groups: Safety Follow-up Period if Device Not Removed

All patients who do not have the IDDD removed (partial or full device) will have safety follow-up visits every 6 months at the site, with the following assessments performed:

- Informed consent
- Symptom-directed PE
- Clinical laboratory tests; only if indicated for a device-related AE
- X-ray monitoring; only for migration or device-related issue
- Concomitant medications, therapies, and procedures; only if indicated for a device-related AE
- AE monitoring only for device-related events

During the 3-year safety follow-up period, the patient may have the device removed at any time, as deemed medically necessary. A post-operative evaluation, including a postoperative check of the incision and collection of safety information, should occur within 1-3 days after the IDDD explantation. An end-of-study safety follow-up via a phone call should be completed within 14 days after the device removal to collect safety information.

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. The training will be documented.

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 Food and Drug Administration (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 and Risk Management database.

10 STATISTICAL ANALYSES

10.1 General Methodology

Statistical analysis will generally be performed by the Biometrics Department of Shire using SAS statistical software (SAS Institute, Cary, NC, USA). Analysis of any PK and health economics and outcomes data will be performed by the Shire Clinical Pharmacology and Pharmacokinetics group and the Health Economics and Outcomes Research groups, respectively. The analysis methods for all other study data (demographic and baseline characteristics, efficacy variables, and safety variables) will be detailed in the statistical analysis plan (SAP). The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the design and objectives of this trial.

Any hypothesis tests will be 2-sided and will be viewed as exploratory. It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

Unless otherwise indicated, all summary statistics will be presented by treatment group (either Q2W or Q4W) to which the patients were randomly assigned (for patients who were initially assigned to Q2W or Q4W group in Study HGT-SAN-093 or patients who were assigned to no-treatment in HGT-SAN-093 and were randomly assigned to Q2W or Q4W in Study SHP-601-201).

All safety data will be summarized descriptively. The change from baseline at each time point for efficacy outcomes will be summarized. Generally, the mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented. If the parametric assumption for the distribution cannot be justified, a non-parametric approach will be utilized to estimate the treatment difference and the corresponding 95% confidence interval (ie, median difference or Hodges–Lehmann estimator and the corresponding confidence intervals). Developmental quotients will be computed as a ratio, expressed as a percentage using the age-equivalent score divided by the age at testing (ie, [age-equivalent score/chronological age] x 100). Developmental delay scores will be calculated as the age-equivalent score minus the chronological age. Additional efficacy analyses in the subgroups of patients who received treatment or no treatment in Study HGT-SAN-093 will be performed.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis. The data included for treated patients in HGT-SAN-093 starts from the baseline of Study HGT-SAN-093 and for patients who received no treatment in HGT-SAN-093 from the baseline of Study SHP-610-201. Baseline is the assessment obtained prior to the first dose of HGT-1410.

10.2 Determination of Sample Size

As this is an extension study of Study HGT-SAN-093, any patients who enrolled and completed that study are eligible to enroll in Study SHP-601-201, and no statistical estimation for sample size calculation was performed. A maximum sample size of 21 patients in this study is expected based on the sample size in Study HGT-SAN-093.

10.3 Method of Assigning Study Subjects to Treatment Groups

Patients who were randomized to receive Q2W or Q4W dosing in Study HGT-SAN-093 (Groups 1 and 2, respectively) will maintain their assigned dosing regimen in Study SHP-610-201.

Patients who were randomized to receive no-treatment in Study HGT-SAN-093 (Group 3) will be re-randomized in a 1:1 allocation ratio via a computer-generated randomization schedule to receive Q2W or Q4W dosing regimen (Groups 3A or 3B, respectively) in Study SHP-610-201. To help ensure balance between the dose groups with respect to age at Baseline, the randomization will be stratified by age group (≤30 months and >30 months).

10.4 Population Description and Exposure

10.4.1 Analysis Populations

The population for all safety analyses will be the safety population, defined as all patients who had the IDDD implant or received at least one dose of study drug in the extension study. Safety analyses will be conducted according to the treatment received. Device related analyses will be conducted in the subset of patients in the safety population who had the device implanted.

The population for all efficacy analyses will be the intent-to-treat (ITT) population, defined as all randomized patient according to the treatment assigned.

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

10.4.2 Subject Disposition

The number of patients screened; the number and proportion of patients randomized, included in the safety population, completed the study, and discontinued prematurely will be presented in a summary table by treatment group; reasons for discontinuation/withdrawal will also be summarized.

10.4.3 Protocol Deviations

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

10.4.4 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by the individual treatment group and the overall HGT-1410 treatment group for the safety population.

10.4.5 Treatment Compliance and Extent of Exposure

The total number of doses of study drug, the number of doses received via IDDD, the number of doses received via LP, the average duration of IT administration and treatment compliance will be summarized by treatment group for the safety population.

The duration of IT administration is calculated by subtracting the IT administration start time from the IT administration end time.

Treatment compliance is defined as: [(Number of Complete IT administrations) ÷ (Expected Number of IT administrations)] * 100.

10.5 Analysis of Efficacy

The analysis of efficacy data will be based on the ITT population.

10.5.1 Primary Analysis

The primary objective of this study is to evaluate long-term safety of HGT-1410 in patients with MPS-III. Therefore the primary analysis will be discussed in the safety analysis section, Section 10.7.

10.5.2 Secondary Efficacy Analysis

10.5.2.1 Bayley Scales of Infant Development, Third Edition/Kaufman Assessment Battery for Children, Second Edition

The observed values and changes from baseline in DQ, age equivalent, and developmental delay scores for each subtest (Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor) will be summarized descriptively for each assessment time point by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean age equivalent and DQ scores for the subtests across time will be presented. A trellis plot of the age-equivalent and DQ scores within each patient will be presented. Furthermore, a spaghetti plot of the cognitive age-equivalent score against chronological age will be presented.

The KABC-II is an alternative to BSID-III. The KABC-II cognitive DQ, age-equivalent, and developmental delay scores will be combined with the corresponding BSID-III scores and summarized at each assessment time point as described above. Most of the patients will have either only BSID-III data or KABC-II data. If a patient has data obtained by each of these methods, then the method for which data is available at both baseline and post-baseline time points will be used when combining the DQ scores and age-equivalent scores.

10.5.2.2 Vineland Adaptive Behavior Scales, Second Edition

Tabular summaries of the raw scores for each domain, the average domain raw scores, the mean age equivalent score and the corresponding overall DQ scores and the corresponding change from baseline will be presented for each assessment time point by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean raw scores for the domains across time will be presented. In addition, a trellis plot of the raw scores within each patient will be presented. Similar plots will be presented for the average domain raw scores, the mean age equivalent score and the overall DQ score. A spaghetti plot of mean age equivalent score against chronological age will also be presented.

10.5.2.3 Brain MRI

Although several MRI parameters will be captured, the analysis will focus primarily on the grey matter volume, the white matter volume and the intracranial CSF volume (ventricles plus additional CSF space). The observed values and changes from baseline will be summarized for each assessment time by treatment group (Q2W and Q4W group). The mean difference in the change at each time point between the 2 treatment groups and the corresponding 95% confidence interval of the mean difference will be presented.

Graphical plots of mean MRI parameter levels across time will be presented. In addition, Trellis plots of MRI parameters across time for each patient will be presented. A spaghetti plot of grey matter volume against chronological age will also be presented.

10.5.3 Subset Analyses

Exploratory tabular and graphical analyses as described above for efficacy endpoints will be performed both by treatment group and whether or not the patient received treatment or no treatment in Study HGT-SAN-093 (4 groups).

10.5.4 Exploratory Analyses

[redacted]

10.5.5 Analysis of Health Status

Health status will be assessed by the ITQoL. The observed value and change from baseline in ITQOL scale scores will be summarized descriptively for each assessment time by treatment group (Q2W and Q4W groups). Graphical plots of mean scores across time will be presented.

10.5.6 Analysis Health Economics and Outcomes Research

Descriptive statistics, including N, mean, median, and range (for continuous variables), and N and proportions (for categorical variables), for key HCUQ variables, including the number of emergency room visits, caregiver employment status (FT, PT, and NW), and the number of hours of additional paid help needed by caregivers, over the course of the study. A detailed description of analyses may be provided in a separate pharmacoeconomic analysis plan.

10.6 Analysis of Pharmacokinetic and Pharmacodynamic Data

10.6.1 Pharmacokinetic Measurement and Parameters

The pharmacokinetic population will be used to perform the analysis of the pharmacokinetic data. HGT-1410 concentrations in all collected serum samples will be measured and reported. Individual patient HGT-1410 serum concentration-time profiles will be presented. Individual pharmacokinetic parameters will be derived by a noncompartmental analysis and reported. The actual pharmacokinetic blood sample collection times will be used to determine the individual patient HGT-1410 serum concentration-time profiles. Pharmacokinetic parameters will be calculated if sufficient HGT-1410 concentration-time points exist to derive values. Individual patient CSF HGT-1410 concentrations at each collection time point will be reported.

Pharmacokinetic parameters calculated will include:

- C_{max}
- t_{max}
- $AUC_{0\text{-}last}$
- $AUC_{0\text{-}\infty}$
- λ_Z
- $t_{1/2}$ calculated as $0.693/\lambda_Z$
- $CL/_F$
- V_z/F

10.6.2 Pharmacodynamic Analyses

The levels of GAG in CSF and urine are pharmacodynamic endpoints. Analyses of pharmacodynamic endpoints will be performed in the safety population.

The observed values and changes from baseline in CSF GAG levels will be summarized for each assessment time by treatment group (Q2W and Q4W group). Graphical plot(s) of mean CSF GAG levels across time will be presented. Additionally, Trellis plots of CSF GAG levels across time for each patient will be presented. Furthermore, CSF parameters will be plotted across time for each patient such that the values before and after the first instance of antibody positive status will be indicated using different colors.

The urine GAG levels will be analyzed in a manner similar to that described for CSF data.

10.7 Analysis of Safety

All analyses of safety data will be descriptive and based on the Safety population.

10.7.1 Adverse Events

Once the patient has signed the informed consent form, AEs will be recorded throughout the study and at early termination. AEs will be coded using Medical Dictionary for Regulatory Affairs (MedDRA).

Treatment-emergent AEs, defined as all AEs from the time of initial IDDD implantation (or first dose if no IDDD implant), to the safety follow-up visit, defined as the last patient visit in the study during the treatment period, will be summarized. For each treatment group, the number and percentage of patients having an AE and the number of events, by system organ class (SOC) and preferred term will be presented. Treatment-emergent AEs will also be summarized by severity and degree of relationship to study drug. In the case of multiple occurrences of the same AE (at the preferred term level) in an individual patient, the AE that is classified as the most severe (ie, maximum severity) will be identified for the analysis by severity and the AE that has the closest relationship to study drug/procedure will be identified for the analysis by relationship. In general, an AE will be considered a treatment-emergent AE if it cannot be definitively categorized otherwise by documentation that its onset preceded either IDDD surgery or first dose.

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

10.7.1.1 Investigational Product

Treatment-emergent AEs deemed by the investigator to be related to HGT-1410 will be summarized by presenting the number and percentage of patients having an AE and the number of events, by SOC and preferred term.

10.7.1.2 IDDD and Surgical Procedure–related AEs

Intrathecal drug delivery devices and procedure-related AEs will be summarized within MedDRA SOC by preferred term. Separate tabulations will be provided for AEs related to the IDDD, device surgical procedure, and IT administration process.

Intrathecal drug delivery device and procedure related events will be analyzed in the subset of patients in the safety population who underwent surgery for IDDD implantation.

10.7.2 Clinical Laboratory Evaluation

The measurements of each laboratory parameter (serum chemistry, hematology, urinalysis and CSF) and the corresponding normal ranges will be converted to Standard International (SI) units, if needed.

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

If more than one laboratory result is reported per assessment time per parameter, the last non-missing result will be selected for analysis.

10.7.3 ECG Evaluations

The observed values and changes from baseline for continuous variables will be summarized for each assessment time by treatment group. Categorical variables, ie, sinus rhythm and atrial/ventricular hypertrophy, will be summarized in terms of number and percentage of patients in each response category for each assessment time from baseline.

10.7.4 Vital Signs

The observed values and changes from baseline for IT-administration vital signs parameters will be summarized by treatment group. The IT-administration vital signs will also be presented in a trellis plot so that the vital signs data for each IT-administration within a patient will be presented on a single page.

10.7.5 Anti-rhHNS Antibody in Serum and CSF

Serum and CSF anti-rhHNS antibody status (ie, positive or negative) at each assessment time from baseline will be summarized in terms of counts and proportion for the treatment groups. Additionally, semi-logarithmic plot of serum and CSF anti-rhHNS antibody titers across the study visits in the patients exhibiting seropositivity will also be presented.

10.7.6 Concomitant Medications

Concomitant medications will be coded using the WHO-DD. The concomitant medications that occur from the time of the surgery for IDDD implantation to the safety follow-up visit, defined as the last patient visit in the study during the treatment period, will be summarized by therapeutic class and preferred term.

10.7.7 Other Observations Related to Safety

10.7.7.1 IDDD Performance

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

The proportion of patients with at least 1 device failure and/or malfunction, as well as the number of and reasons for device failures/malfunctions will be summarized. The rate of device failures/malfunctions and 95% confidence interval will also be estimated. The time from initial implant surgery to first device failure and/or malfunction will be summarized. Patients without a device failure/malfunction will be censored at their last study drug injection date. A by-patient listing of the device failure/malfunction data will be displayed.

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

10.8 Statistical/Analytical Issues

10.8.1 Adjustment for Covariates

No statistical modeling or covariate adjustment is planned due to the small sample size.

10.8.2 Handling of Dropouts or Missing Data

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

10.8.3 Interim Analyses and Data Monitoring

Interim analyses may be conducted before trial completion for safety monitoring, regulatory reporting or general study planning purposes. Analyses will be descriptive in nature, with no formal comparisons planned and no hypotheses formally tested. An independent DMC will be established to provide an ongoing, independent review and assessment of patient data, and to safeguard the interests and safety of the participating patients in the study (see Section 11.8). An analysis of the data for DMC review will occur at specific times during the study as specified in the DMC charter. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.

10.8.4 Multicenter Studies

Data from all centers that participate in this protocol will be combined so that an adequate number of patients will be available for analysis. In order to maintain desirable level of inter-rater reliability for BSID-III/KABS-II and VABS-II assessments/interviews, standardized training of the raters and parents will be conducted. Furthermore, a central reader will evaluate all MRI data.

10.8.5 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed.

10.8.6 Sensitivity Analyses

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

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

11.2 Institutional Review Board or Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/EC 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.

The protocol and any applicable documentation will be submitted or notified to the relevant Regulatory Authorities in accordance with the regulations of the countries involved in the trial.

Status reports must be submitted to the IRB/EC at least once per year. The IRB/EC must be notified of completion of the study. Within 3 months of study completion or termination, a final report must be provided to the IRB/EC. 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/EC, including a list of all reports and documents submitted. Adverse events that are reported to the US FDA (Investigational New Drug/UADE Safety Reports) or other regulatory agencies must be submitted promptly to the IRB/EC.

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

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

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the 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).

After reading the informed consent document, the patient or 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, 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 or 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 of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark) or by the personally dated signature of the patient's parent(s) or the patient's legally authorized representative. 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 or 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 patient initials will be recorded in the eCRF, and if the patient name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. 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/EC, 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

11.7.1 Case Report Forms

Case report forms (paper or electronic) are provided for each patient. All forms must be filled out by authorized study personnel. All corrections to the original 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 resigning the eCRF.

11.7.2 Critical Documents

Before Shire initiates the trial (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 12 months of study initiation)
- Copy of Investigator and sub-Investigator(s) current medical license (indicating license number and expiration date)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/EC clearly identifying the documents reviewed by name, number and date of approval or regarding approval: protocol, any amendments, Patient Information/Informed Consent Form, and any other written information to be provided regarding patient recruitment procedures
- Copy of IRB-/EC-approved Patient Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval)
- Current list of IRB/EC Committee members/constitution (dated within 12 months prior to study initiation)
- Financial Disclosure Form signed by Investigator and sub-Investigator(s)
- Current laboratory reference ranges (if applicable)
- Certification/QA scheme/other documentation (if applicable)

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

11.8 Data Monitoring Committee

An independent DMC will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study during the treatment period. The DMC will consist of a biostatistician and 2 clinical experts.

It is anticipated that there will be scheduled meetings annually during the treatment period of the study. The first meeting will be an orientation meeting and will take place prior to the start of the study. Subsequent meetings will occur at specific times during the study as specified in the DMC charter. The final meeting will be conducted when all patients have completed treatment period of the study for a comprehensive safety overview of the study. A special DMC meeting will be convened if the safety-related study stopping rules are met during the treatment period of the study (see Section 7.16).

The DMC will adhere to a prospectively determined charter, which will be written by Shire and approved by the DMC. The charter will define the responsibilities of the DMC and Shire, describe the conduct of the meetings and define the data sets to be reviewed. The DMC will also be notified of all IDDD failures and IDDD-related complications at times defined in the DMC charter.

The DMC will be notified of all IDDD failures and IDDD-related complications at times defined in the DMC 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/EC 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/EC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/EC 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/EC. 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 will be granted for this study.

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

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

11.11 Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable 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 product may be made at any time. Conditions that may warrant termination of the study or site include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the 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/EC, or the Sponsor (or its designee) may request access to all source documents, eCRFs, and other study documentation for onsite audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, crosschecking with source documents, and clarification of administrative matters may be performed.

11.13 Data Generation and Analysis

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

Adverse events and medical history 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 and safety parameters.

11.14 Retention of Data

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

11.15 Financial Disclosure

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

11.16 Publication and Disclosure Policy

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

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

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

Shire may perform analyses of interim or final locked study data for purposes of publication.

12 LIST OF REFERENCES

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Appendix 1 Study Schedule of Events for Group 1: Maintaining HGT-1410 Q2W

Procedure	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				Follow-up
	Weeks[a]																				
	50	52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	122, 124, 126, 128, 130	132	134, 136, 138, 140, 142	144	146, 148, 150, 152, 154	156	158, 160, 162, 164, 166	168	172[h]
Informed consent	•																				
Review of inclusion/exclusion criteria	•																				
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Full PE including height, weight, and head circumference					•				•				•				•				•
Symptom-directed PE	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•	•
BSID-III/KABC-II[c]					•				•				•				•				•
VABS-II					•				•				•				•				•
ITQoL[d]					•				•				•				•				•
HCUQ					•				•				•				•				•
ECG[e]									•								•				•
Hematology			•		•		•		•		•		•		•		•		•		•
Serum chemistry			•		•		•		•		•		•		•		•		•		•
Urinalysis			•		•		•		•		•		•		•		•		•		•
MRI of the head									•								•				
MRI of liver and spleen									•								•				
HGT-1410 administration	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Standard CSF safety labs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
CSF sample for GAG testing			•		•		•		•		•		•		•		•		•		•
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•		•		•		•		•		•		•
Serum PK sampling[g]									•												
CSF sample for storage for biomarkers	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Con meds, therapies, and procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Procedure	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				Follow-up
	Weeks[a]																				
	50	52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86. 88. 90. 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116, 118	120	122, 124, 126, 128, 130	132	134, 136, 138, 140, 142	144	146, 148, 150, 152, 154	156	158, 160, 162, 164, 166	168	172[h]
AE monitoring	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT= activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; ECG=electrocardiogram; GAG= glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life Questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs during the treatment period will be obtained immediately prior to IT dosing.

[c] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[d] For patients ≤5 years of age

[e] ECGs are to be performed after study drug administration.

[f] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[g] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[h] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 172.

Appendix 2 Study Schedule of Events for Group 2: Maintaining HGT-1410 Q4W

Procedure	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																					Follow-up
	Weeks[a]																					
	52	56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124, 128	132	136, 140	144	148, 152	156	160, 164	168	172[a]
Informed consent	•																					
Review of inclusion/exclusion criteria	•																					
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Full PE including height, weight, and head circumference					•				•				•				•				•	
Symptom-directed PE	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/KABC-II[c]					•				•				•				•				•	
VABS-II					•				•				•				•				•	
ITQoL[d]					•				•				•				•				•	
HCUQ					•				•				•				•				•	
ECG[e]									•								•				•	
Hematology			•		•		•		•		•		•		•		•		•		•	•
Serum chemistry			•		•		•		•		•		•		•		•		•		•	•
Urinalysis			•		•		•		•		•		•		•		•		•		•	•
MRI of the head									•								•					
MRI of liver and spleen									•								•					
HGT-1410 administration	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[f]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing			•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[g]									•													
CSF sample collection for storage for biomarkers	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, and procedures	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; con meds=concomitant medications; ECG=electrocardiogram; GAG= glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second

Procedure	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																				Follow-up
	Weeks[a]																				
	52	56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124, 128	132	136, 140	144	148, 152	156	160, 164	168	172[h]

Edition; MRI=magnetic resonance imaging; PD=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs during the treatment period will be obtained immediately prior to IT dosing.

[c] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[d] For patients ≤5 years of age

[e] ECGs are to be performed after study drug administration.

[f] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[g] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection.

[h] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 172.

Appendix 3 Study Schedule of Events for Group 3A: Initiating HGT-1410 Q2W

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
Procedure	**Days**		**Weeks[a]**																																				
	-21 to -7	Postop check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]
Informed consent	•																																						
Review of inclusion/exclusion criteria	•																																						
Randomization	•																																						
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigator assessment of vision and hearing ability	•																																						
Full PE including height, weight, and head circumference	•[c]														•												•				•				•				•	
Symptom-directed PE		•	•	•	•	•	•	•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•	•		•	•	•		•	•	•		•	•		•
BSID-III/KABC-II[d]	•[e]														•												•				•				•				•	
VABS-II	•[e]														•												•				•				•				•	
ITQoL[f]	•[e]														•												•				•				•				•	
HCUQ	•[e]														•												•				•				•				•	
ECG[g]	•		•		•		•		•		•		•		•												•								•				•	
Hematology	•		•		•		•		•		•		•		•						•						•		•		•		•		•		•		•	•
PT and aPTT	•																																							
Serum chemistry	•		•		•		•		•		•		•		•						•						•		•		•		•		•		•		•	•
Urinalysis	•		•		•		•		•		•		•		•						•						•		•		•		•		•		•		•	•
MRI of the head	•[h]														•												•								•				•	

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
Procedure	**Days**		**Weeks[a]**																																				
	-21 to -7	Postop check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]
MRI of liver and spleen	•[h]														•												•							•					
IDDD implantation	•																																						
X-ray to check IDDD placement	•																																						
Postoperative check of IDDD incision		•[i]																																					
HGT-1410 administration			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing	•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•	
Urine sample for GAG			•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•		•		•		•						•						•						•		•		•		•		•		•	
Serum PK sampling[k]			•																								•							•					
CSF PK sampling[k]			•																								•												
CSF sample for storage for biomarkers	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, and procedures	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
AE monitoring	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; ECG=electrocardiogram; GAG=glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																				Follow-up
Procedure	Days		Weeks[a]																																				
	-21 to -7	Postop check	Day 0 Week 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50, 52, 54, 56, 58	60	62, 64, 66, 68, 70	72	74, 76, 78, 80, 82	84	86, 88, 90, 92, 94	96	98, 100, 102, 104, 106	108	110, 112, 114, 116,118	120	124[l]

sulfatase; ITQoL=Infant Toddler Quality of Life Questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PD=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs at Weeks 0-48 will be obtained immediately prior to IT dosing; at 15, 30, 45, 60, 90, and 120 minutes; and at 2.5, 3, and 4 hours after dosing. Vital signs at Weeks 50-120 will be obtained immediately prior to IT dosing.

[c] Head circumference will be measured only at screening.

[d] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[e] Cognitive assessments are to be performed before IDDD implantation. The Week 48 assessments from Study HGT-SAN-093 will be used as the baseline assessments in Study SHP-610-201. If the Week 48 assessments from Study HGT-SAN-093 are missing, these assessments will need to be performed prior to IDDD implantation in the extension study.

[f] For patients ≤5 years of age

[g] ECGs are to be performed after study drug administration.

[h] If scheduling does not permit the MRI assessments to be performed during IDDD implantation (under the same general anesthetic), then these procedures should be done before the first dose of HGT-1410 at Day -1. This would require administration of anesthesia.

[i] Postoperative check of IDDD incision (1-3 days after operation) along with con med, therapies, and procedures and AE monitoring.

[j] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[k] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection. CSF PK samples to be obtained immediately prior to IT injection, then at 4 and 48 hours following completion of the IT injection.

[l] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments for Week 124.

Appendix 4 Study Schedule of Events for Group 3B: Initiating HGT-1410 Q4W

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																					Follow-up
Procedure	**Days**		**Weeks[a]**																					
	-21 to -7	Postop check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[l]
Informed consent	•																							
Review of inclusion/ exclusion criteria	•																							
Randomization	•																							
Vital signs[b]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigator assessment of vision and hearing ability	•																							
Full PE including Height, Weight, and Head Circumference	•[c]						•				•				•				•				•	
Symptom-directed PE		•	•	•	•	•		•	•	•		•	•	•		•	•	•		•	•	•		•
BSID-III/ KABC-II[d]	•[e]						•				•				•				•				•	
VABS-II	•[e]						•				•				•				•				•	
ITQoL[f]	•[e]						•				•				•				•				•	
HCUQ	•[e]						•				•				•				•				•	
ECG[g]	•		•	•	•	•	•				•								•				•	
Hematology	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
PT and aPTT	•																							
Serum chemistry	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
Urinalysis	•		•	•	•	•	•		•		•		•		•		•		•		•		•	•
MRI of the head	•[h]						•				•								•					
MRI of liver and spleen	•[h]						•				•								•					
IDDD implantation	•																							
X-ray to check IDDD placement	•																							
Postoperative check of IDDD incision		•[i]																						

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																				Follow-up
Procedure	**Days**		**Weeks[a]**																				
	-21 to -7	Postop check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[l]
HGT-1410 administration			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Standard CSF safety labs[j]	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
CSF sample for GAG testing	•		•	•	•	•	•	•	•	•	•		•		•		•		•		•		•	
Urine sample for GAG			•	•	•	•	•	•	•	•	•		•		•		•		•		•		•	
Anti-rhHNS Ab testing (serum and CSF) and CSF biomarker testing			•	•	•		•		•		•		•		•		•		•		•		•	
Serum PK sampling[k]			•								•								•					
CSF PK sampling[k]			•								•													
CSF sample collection for storage for biomarkers	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Con meds, therapies, & procedures	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Adverse event monitoring	•	•[i]	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Abbreviations: Ab=antibody; AE=adverse event; aPTT=activated partial thromboplastin time; BSID-III=Bayley Scales of Infant and Toddler Development, Third Edition; con meds=concomitant medications; CSF=cerebrospinal fluid; ECG=electrocardiogram; GAG= glycosaminoglycan; HCUQ=Healthcare Utilization Questionnaire; HNS=heparan N-sulfatase; ITQoL=Infant Toddler Quality of Life Questionnaire; KABC-II=Kaufman Assessment Battery for Children, Second Edition; MRI=magnetic resonance imaging; PD=pharmacodynamics; PE=physical examination; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N-sulfatase; VABS-II=Vineland Adaptive Behavior Scale, Second Edition

[a] Time point for weeks refers to the start of the week.

[b] Vital signs at Weeks 0-48 will be obtained immediately prior to IT dosing; at 15, 30, 45, 60, 90, and 120 minutes; and at 2.5, 3, and 4 hours after dosing. Vital signs at Weeks 50-120 will be obtained immediately prior to IT dosing.

[c] Head circumference will only be measured at screening.

[d] KABC-II will be used if and when a child ages out of the BSID-III and his/her cognitive status permits the use of the KABC-II.

[e] Cognitive assessments are to be performed before IDDD implantation. The Week 48 assessments from Study HGT-SAN-093 will be used as the baseline assessments in Study SHP-610-201. If the Week 48 assessments from Study HGT-SAN-093 are missing, these assessments will need to be performed prior to IDDD implantation in the extension study.

[f] For patients ≤5 years of age

[g] ECGs are to be performed after study drug administration.

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																			Follow-up
Procedure	Days		Weeks[a]																			
	-21 to -7	Postop check	Day 0 Week 0	4, 8	12	16, 20	24	28, 32	36	40, 44	48	52, 56	60	64, 68	72	76, 80	84	88, 92	96	100, 104	108	112, 116	120	124[l]

[h] If scheduling does not permit the MRI assessments to be performed during IDDD implantation (under the same general anesthetic), then these procedures should be done before the first dose of HGT-1410 at Day -1. This would require administration of anesthesia.

[i] Postoperative check of IDDD incision (1-3 days after operation) along with con med, therapies, and procedures and AE monitoring.

[j] CSF sample should be sent for clinical laboratory analysis before each dose of HGT-1410.

[k] Serum PK samples to be obtained immediately prior to IT injection, then at 0.5, 1, 2, 4, 8, 12, 24, and 48 hours following completion of IT injection. CSF PK samples to be obtained immediately prior to IT injection, then at 4 and 48 hours following completion of the IT injection.

[l] If the patient withdraws from the study, the IDDD will be removed and the patient will be asked to complete the assessments done at Week 124.

Appendix 5 Study Schedule of Events for the Safety Follow-up Period for Patients with Implanted Partial or Full Device After Treatment Completion

Procedure	Every 6 Months from Last Visit (±14 Days)[b]	End of Study		
		Device Explantation[e] Day 1	Postoperative Evaluation Days 2-4[f]	Safety Follow-up Call 14 days post device explantation
Informed consent[a]	•			
Symptom-directed PE	•		•	
Hematology[c]	•			
Serum chemistry[c]	•			
Urinalysis[c]	•			
Standard CSF safety labs[c]	•			
X-ray[d]	•			
Con meds, therapies, and procedures	•	•	•	•
Device-related AE monitoring	•	•	•	•
Postoperative check of IDDD incision			•	

Abbreviations: IDDD= intrathecal drug delivery device; PE=physical examination; AE= adverse event

[a] Informed consent will be captured at the first 6 month visit after the end of the treatment period.

[b] From the patient's last follow-up visit and every 6 months thereafter up until the device is removed

[c] To be acquired only as indicated by a device-related AE.

[d] To check IDDD placement or for any device-related AEs.

[e] During the 3-year safety follow-up period, the patient may have the device removed at any time, as deemed medically necessary

[f] Postoperative evaluation can occur within 1-3 days after IDDD explantation.

Appendix 6 Blood and CSF Volumes

	Treatment Period for Patients in Group 1: Maintaining HGT-1410 Every Other Week Dosing																				**Follow-up**	**TOTAL**
	Weeks																					
Procedure	**50**	**52, 54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102, 104, 106**	**108**	**110, 112, 114, 116, 118**	**120**	**122, 124, 126, 128, 130**	**132**	**134, 136, 138, 140, 142**	**144**	**146, 148, 150, 152, 154**	**156**	**158, 160, 162, 164, 166**	**168**	**172**	
CSF (mL)																						
Standard CSF safety labs	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
CSF sample for GAG testing			a		a		a		a		a		a		a		a		a		a	
Anti-rhHNS Ab testing (CSF)			b		b		b		b		b		b		b		b		b		b	
CSF for storage (for biomarkers and Ab testing)	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	
Total CSF Volume	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**660**
Blood (mL)																						
Hematology			2		2		2		2		2		2		2		2		2		2	2	
Serum chemistry			2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.5	
Anti-rhHNS Ab testing (serum)			4		4		4		4		4		4		4		4		4		4		
Serum PK sampling									9														
Total Blood Volume			**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**	**4.5**	**98.5**

Abbreviations: Ab=antibody; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; PK=pharmacokinetics; rhHNS=recombinant human heparan N sulfatase

[a] CSF for GAGs included in CSF storage sample

[b] Anti-rhHNS Ab testing in CSF will be performed on stored samples.

	Treatment Period for Patients in Group 2: Maintaining HGT-1410 Dosing Every 4 Weeks																				**Follow-up**	**TOTAL**
	Weeks																					
Procedure	**52**	**56**	**60**	**64, 68**	**72**	**76, 80**	**84**	**88, 92**	**96**	**100, 104**	**108**	**112, 116**	**120**	**124, 128**	**132**	**136, 140**	**144**	**148, 152**	**156**	**160, 164**	**168**	**172**	
CSF (mL)																							
Standard CSF safety labs	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
CSF sample for GAG testing			a		a		a		a		a		a		a		a		a		a		
Anti-rhHNS Ab testing (CSF)			b		b		b		b		b		b		b		b		b		b		
CSF for storage (for biomarkers and Ab testing)	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
Total CSF Volume	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**		**330**
Blood (mL)																							
Hematology			2		2		2		2		2		2		2		2		2		2	2	
Serum chemistry			2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.5	
Anti-rhHNS Ab testing (serum)			4		4		4		4		4		4		4		4		4		4		
Serum PK sampling									9														
Total Blood Volume			**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**		**8.5**	**4.5**	**98.5**

Abbreviations: Ab=antibody; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; PK=pharmacokinetics; rhHNS=recombinant human heparan N sulfatase

a CSF for GAGs included in CSF storage sample

b Anti-rhHNS Ab testing in CSF will be performed on stored samples.

	IDDD Implantation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																			Follow-up	TOTAL
Procedure	**Days**		**Weeks**																																				
	-21 to -7	**Postop check**	**Day 0, Week 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50, 52, 54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102, 104, 106**	**108**	**110, 112, 114, 116, 118**	**120**	**124**	
CSF (mL)																																							
Standard CSF safety labs	3		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
CSF sample for GAG testing	a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		a		
Anti-rhHNS Ab testing (CSF)			b		b		b		b						b						b						b		b		b		b		b		b		
CSF PK sampling (Appendix 7)			4																								4												
CSF for storage (for biomarkers and Ab testing)	8		8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
Total CSF Volume	**11**		**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**		**690**
Blood (mL)																																							
Hematology	2		2		2		2		2		2		2		2						2						2		2		2		2		2		2	2	
Serum chemistry	2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						2.5						2.5		2.5		2.5		2.5		2.5		2.5	2.5	
PT and aPTT (coagulation)	1.8																																						
Anti-rhHNS Ab testing (serum)			4		4		4		4						4						4						4		4		4		4		4		4		
Serum PK sampling (Appendix 7)			9																								9						9						

	IDDD Implantation Period		Treatment Period for Patients in Group 3A: Initiating HGT-1410 Every Other Week Dosing																																					Follow-up	TOTAL
Procedure	**Days**		**Weeks**																																						
	-21 to -7	**Postop check**	**Day 0, Week 0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50, 52, 54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102, 104, 106**	**108**	**110, 112, 114, 116, 118**	**120**	**124**	
Total Blood Volume	**6.3**		**17.5**		**8.5**		**8.5**		**8.5**		**4.5**		**4.5**		**8.5**						**8.5**						**17.5**		**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**	**4.5**	**157.3**

Abbreviations: Ab=antibody; aPTT=activated partial thromboplastin time; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; IDDD=intrathecal drug delivery device; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N sulfatase

[a] CSF for GAGs included in CSF storage sample

[b] Anti-rhHNS Ab testing in CSF will be performed on stored samples.

	IDDD Implant-ation Period		Treatment Period for Patients in Group 3B: Initiating HGT-1410 Dosing Every 4 Weeks																					Follow-up	TOTAL
Procedure	**Days**																								
	-21 to -7	**Postop check**	**Day 0, Week 0**	**4, 8**	**12**	**16, 20**	**24**	**28, 32**	**36**	**40, 44**	**48**	**52, 56**	**60**	**64, 68**	**72**	**76, 80**	**84**	**88, 92**	**96**	**100, 104**	**108**	**112, 116**	**120**	**124**	
CSF (mL)																									
Standard CSF safety labs	3		3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		
CSF sample for GAG testing	a		a	a	a	a	a	a	a	a	a		a		a		a		a		a		a		
Anti-rhHNS Ab testing (CSF)			b	b	b		b		b		b		b		b		b		b		b		b		
CSF PK sampling (Appendix 7)			4								4														
CSF for storage (for biomarkers and Ab testing)	8		8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8		
Total CSF Volume	**11**		**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**15**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**		**360**
Blood (mL)																									
Hematology	2		2	2	2	2	2		2		2		2		2		2		2		2		2	2	
Serum chemistry	2.5		2.5	2.5	2.5	2.5	2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.5	
PT and aPTT (coagulation)	1.8																								
Anti-rhHNS Ab testing (serum)			4	4	4		4		4		4		4		4		4		4		4		4		
Serum PK sampling (Appendix 6)			9								9								9						
Total Blood Volume	**6.3**		**17.5**	**8.5**	**8.5**	**4.5**	**8.5**		**8.5**		**17.5**		**8.5**		**8.5**		**8.5**		**17.5**		**8.5**		**8.5**	**4.5**	**157.3**

Abbreviations: Ab=antibody; aPTT=activated partial thromboplastin time; CSF=cerebrospinal fluid; GAG=glycosaminoglycan; IDDD=intrathecal drug delivery device; PK=pharmacokinetics; PT=prothrombin time; rhHNS=recombinant human heparan N sulfatase

[a] CSF for GAGs included in CSF storage sample

[b] Anti-rhHNS Ab testing in CSF will be performed on stored samples.

Appendix 7 Pharmacokinetic and Pharmacodynamic Sample Schedule

Drug Administration	PK/PD Sampling Times
	Blood Sampling
HGT-1410 IT injection	Serum PK samples will be obtained at Weeks 0, 48, and 96 for Groups 3a and 3b. Serum PK samples will be obtained at Week 96 for Groups 1 and 2. Immediately prior to IT injection (baseline), then at 0.5, 1, 2, 4, 8, 12, 24, and 48 (Day 2) hours following completion of IT injection. Patients may be discharged from the hospital after the 24-hour blood draw. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); in consultation with the Investigator. Patients will return to the hospital for PK blood sampling at the 48-hour PK time point. Patients will be discharged for home following the last (48-hour) PK time point and following the completion of their final physical examination.
	CSF Sampling
	CSF PK and PK/PD samples will be obtained at Weeks 0 and 48 for Groups 3A and 3B only. Immediately prior to IT injection (baseline), then at 4 hours and 48 hours after the completion of the IT injection. The 4-hour and 48-hour post-dose CSF samples will only be obtained if a functioning IDDD is in place. Patients will either stay locally in a hotel or return home (if they live in close proximity to the hospital); in consultation with the Investigator. Patients will return to the hospital for CSF sampling at the 48 hour time points.

Abbreviations: CSF=cerebrospinal fluid; IDDD=intrathecal drug delivery device; IT=intrathecal; PD=pharmacodynamics; PK=pharmacokinetics

Appendix 8 Expected SOPH-A-PORT Mini S Adverse Device Effects

Procedure-related Complications

- Components handled improperly before, during, or after implantation
- Access port implanted incorrectly
- Catheter positioned improperly
- Injection through septum performed incorrectly
- Injection of incorrect medication through access port
- Injection outside the access port into pocket or subcutaneous tissue or extravasation
- Pocket seroma, hematoma, erosion, or infection
- 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-LP, 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 9 Protocol Amendment Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol SHP-610-201 has been amended to include language to allow for patients to retain a full or partial IDDD in situ after they discontinue or complete the treatment period of the study, at the discretion of the investigator based upon safety assessment. These patients who do not have the IDDD removed at the end of the treatment period will continue to be observed during a safety follow-up period with visits every 6 months to evaluate patient safety of the device up to an additional 3 years or until the device is removed in the last patient.

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 change summary.

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: Patients should have the IDDD removed; however, the Investigator may determine that the device should not be removed upon safety assessment.
Section impacted by this change: Section 4.1, Overall Study Design and Plan
Revised Text: Patients ~~will~~ **should** have the IDDD removed when they discontinue from or complete the **treatment period of the** study, unless the ~~patient is continuing to receive treatment through another mechanism (eg, extension study, expanded access program, commercially available, etc.~~) **investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.**
Other sections impacted by this change: Synopsis, Section 7.4.4, Device Adjustment, Revision, or Removal; Section 8.1.1.2, Post-treatment Assessments; Section 8.2.1.2, Post-treatment Assessments; Section 8.4.1.2, Post-treatment Assessments; Section 8.5.1.2, Post-treatment Assessments

Change: Clarification that safety and efficacy assessments were performed in the treatment period of the study.
Section impacted by this change: Section 4.1, Overall Study Design and Plan
Revised Text: Safety and efficacy assessments will be performed at regular intervals over the approximate 2.5-year duration of **the treatment period of** Study SHP-610-201.
Other sections impacted by this change: Synopsis

Change: Patients who do not have the device removed will be observed for safety during a safety follow-up period with visits every 6 months.
Section impacted by this change: Section 4.1, Overall Study Design and Plan
Revised Text: **Patients who do not have the IDDD removed (partial or full device) at the end of the treatment period will continue to be observed during a safety follow-up period with visits at the site every 6 months to evaluate patient safety of the device until the IDDD has been fully explanted.**
Other sections impacted by this change: Synopsis

Change: The study duration may be longer than 30 months, as for patients in the safety follow-up period will be up to an additional 3 years or until the device is removed in the last patient.
Section impacted by this change: Section 4.3, Study Duration
Revised Text: Patients ~~are expected to participate in this study for up to 30 months. Patients~~ who received HGT-1410 in Study HGT-SAN-093 will undergo a cumulative exposure to HGT-1410 for up to 42 months (168 weeks), whereas patients who received no treatment in Study HGT-SAN-093 will have a cumulative exposure to HGT-1410 for up to 30 months (120 weeks) in Study SHP-610-201. ~~For those~~ **Patients with a partial or full device still in place after completion of the treatment period**~~, patients~~ **may be followed for safety up to an additional 3 years or until the device is removed in the last patient.**
Other sections impacted by this change: Synopsis

Change: Schedule of events added for the safety follow-up period.
Section impacted by this change: Section 4.1 Overall Study Design and Plan
Revised Text: **See Appendix 5 for the Study Schedule of Events for the safety follow-up period for patients with partial or full devices in place after the end of the treatment period.**
Other sections impacted by this change: Section 7, Study Procedures; Section 8, Study Activities, Appendix 5

Change: LPLV defined
Section impacted by this change: Section 4.3, Study Duration
Revised Text: **The LPLV will be the safety follow-up visit after the final device (partial and/or full) is removed from the last patient during the safety follow-up period.**
Other sections impacted by this change: Synopsis

Change: Informed consent will be obtained from patients who did not have the device removed.
Section impacted by this change: Section 7.1, Informed Consent
Revised Text: **After the treatment period ends, informed consent from patients who do not have the IDDD removed (partial or full device) will be obtained for the safety follow-up period.**
Other sections impacted by this change: NA

Change: Clarification regarding x-ray verification during safety follow-up period.
Section impacted by this change: Section 7.4.2 X-ray Verification of Intrathecal Drug Delivery Device Placement
Revised Text: A postoperative X-ray check of the IDDD will be performed following surgery for Groups 3A and 3B to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The X-rays may be performed to check placement**, migration, or malfunction** of the device, as needed, throughout the **treatment period or safety follow-up period of** the study. At a minimum, the date of the X-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during **the treatment period of** the study, additional X-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray will be performed to assess the potential cause of malfunction. Fluoroscopy should be used during device implantation procedures.
Other sections impacted by this change: NA

Change: Symptom-directed physical examinations to be performed during the safety follow-up period.
Section impacted by this change: Section 7.11.2 Physical Examination, Including Height, Weight, and Head Circumference
Revised Text: During the study, physical examinations will be performed at the time points indicated in the Schedules of Events. For Groups 1 and 2, full physical examinations will be conducted at Weeks 96, 120, 144, and 168, and for Groups 3A and 3B, full physical examinations will be conducted during the IDDD implantation period and at Weeks 24, 48, 72, 96, and 120. The remainder of physical examinations will be symptom-directed**, including examinations during the safety follow-up period in patients who do not have the**

IDDD removed (partial or full device) at the end of the treatment period.
Other sections impacted by this change: NA

Change: Clinical laboratory testing only performed for device-related AEs during the safety follow-up period.
Section impacted by this change: Section 7.11.4, Clinical Laboratory Testing
Revised Text: **Clinical laboratory testing will only be performed when indicated for a device-related AE for patients who do not have the IDDD removed (partial or full device) at the end of the treatment period.**
Other sections impacted by this change: NA

Change: Final evaluation in the safety follow-up period defined.
Section impacted by this change: Section 7.13.6.1, Adverse Event Monitoring and Period of Observation
Revised Text: For the purposes of this study, the period of observation extends from the time at which the patient, the patient's parent(s), or the patient's legally authorized representative gives informed consent until the patient's final evaluation of the study. For safety purposes, the final evaluation **for the treatment period** will be defined as the follow-up evaluation performed approximately 30 days after the last dose for patients who complete the study. **The final evaluation in the safety follow-up period for patients who do not have the IDDD removed (full or partial device) is defined as the follow-up evaluation performed for up to 3 years after the treatment period ends.**
Other sections impacted by this change: NA

Change: Study discontinuation process defined.
Section impacted by this change: Section 7.15.1, Study Discontinuation Process
Revised Text: **If the patient is discontinued from the study, the IDDD should be removed and a modified end-of-study visit should be completed within 30 days after withdrawal. These visits may be combined into 1 visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. The end-of-study visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution.** **If the investigator determines that the IDDD should not be removed from the patient**

based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit. This last treatment period visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution. Once the patient completes their last treatment period visit, they will return for their first safety follow-up visit in 6 months. The patient will continue in the safety follow-up period with a clinic visit every 6 months for up to 3 years or until the device is removed in the last patient. An end-of-study follow-up via a phone call should be completed within 14 days after the device removal to collect safety information (refer Section8.6;Appendix 5).
Other sections impacted by this change: NA

Change: Assessments during safety follow-up period if device not removed described.
Section impacted by this change: Section 8.6, All Groups: Safety Follow-up Period if Device Not Removed
Revised Text: **All patients who do not have the IDDD removed (partial or full device) will have safety follow-up visits every 6 months at the site, with the following assessments performed:** • **Informed consent** • **Symptom-directed PE** • **Clinical laboratory tests; only if indicated for a device-related AE** • **X-ray monitoring; only for migration or device-related issue** • **Concomitant medications, therapies, and procedures; only if indicated for a device-related AE** • **AE monitoring only for device-related events** **During the 3-year safety follow-up period, the patient may have the device removed at any time, as deemed medically necessary. A post-operative evaluation, including a postoperative check of the incision and collection of safety information, should occur within 1-3 days after the IDDD explantation. An end-of-study safety follow-up via a phone call should be completed within 14 days after the device removal to collect safety information.**
Other sections impacted by this change: Section 7.16, Safety-Related Study Stopping Rules

Change: Clarification regarding statistical analysis of TEAEs and treatment period.
Section impacted by this change: Section 10.7.1, Adverse Events
Revised Text: Treatment-emergent AEs, defined as all AEs from the time of initial IDDD implantation (or first dose if no IDDD implant), to the safety follow-up visit, defined as the last patient visit in the study **during the treatment period**, will be summarized.
Other sections impacted by this change: NA

Change: Clarification regarding statistical analysis of concomitant medications and treatment period.
Section impacted by this change: Section 10.7.6, Concomitant Medications
Revised Text: Concomitant medications will be coded using the WHO-DD. The concomitant medications that occur from the time of the surgery for IDDD implantation to the safety follow-up visit, defined as the last patient visit in the study **during the treatment period**, will be summarized by therapeutic class and preferred term.
Other sections impacted by this change: NA

Change: Language added indicating interim analysis may be performed.
Section impacted by this change: Section 10.8.3, Interim Analyses and Data Monitoring
Revised Text: **Interim analyses may be conducted before trial completion for safety monitoring, regulatory reporting or general study planning purposes. Analyses will be descriptive in nature, with no formal comparisons planned and no hypotheses formally tested.** ~~No formal interim analysis or interim statistical testing for early stopping of the trialis planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting or general study planning purposes.~~An independent DMC will be established to provide an ongoing, independent review and assessment of patient data, and to safeguard the interests and safety of the participating patients in the study (see Section 11.8). An analysis of the data for DMC review will occur at specific times during the study as specified in the DMC charter. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.
Other sections impacted by this change: NA

Change: Clarification that the DMC monitoring will only be conducted during the treatment period.
Section impacted by this change: Section 11.8, Data Monitoring Committee
Revised Text: An independent DMC will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating patients in the study **during the treatment period**. The DMC will consist of a

biostatistician and 2 clinical experts. It is anticipated that there will be scheduled meetings annually during the **treatment period**~~conduct~~ of the study. The first meeting will be an orientation meeting and will take place prior to the start of the study. Subsequent meetings will occur at specific times during the study as specified in the DMC charter. The final meeting will be conducted when all patients have completed **treatment period of** the study for a comprehensive safety overview of the study. A special DMC meeting will be convened if the safety-related study stopping rules are met **during the treatment period of the study** (see Section 7.16).
Other sections impacted by this change: Section 7.16, Safety-Related Study Stopping Rules

Appendix 10 Protocol Signature Page

Study Title:	An Open-Label Extension of Study HGT-SAN-093 Evaluating the Safety and Efficacy of HGT-1410 (Recombinant Human Heparan N Sulfatase) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Mucopolysaccharidosis Type IIIA Disease
Study Number:	SHP-610-201
Final Date:	25 January 2017

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

[redacted] _____ [redacted]
Signature **Date**

[redacted], DO
_____
Printed Name