STATISTICAL ANALYSIS PLAN

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

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Original: 22 November 2016
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Protocol Number:	SHP-610-201	
Protocol Version/Date	Amendment 1	17 December 2015
Indication:	Long-term Treatment of Mucopolysaccharidosis Type IIIA (MPS IIIA or Sanfilippo Syndrome Type A)	
Study Phase	IIb	
SAP Author	[redacted], PhD	
SAP Analysis Type	Final Analysis	
SAP Version/Date	Final	November 22, 2016

SHP-610-201 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES:

The planned statistical analyses are appropriate for the analysis of the SHP-610-201 data. These analyses are in accordance with the study objectives and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS

1.1 Abbreviations

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration 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
BSID-III	Bayley Scales of Infant Development, Third Edition
CL/F	total body clearance for extravascular administration divided by the fraction of dose absorbed
C_{max}	maximum concentration occurring at t_{max}
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
DQ	developmental quotient
eCRF	electronic case report form
ECG	electrocardiogram
GAG	glycosaminoglycan
HGT	human genetic therapies
HS	heparan sulfate
IDDD	intrathecal drug delivery device
IT	intrathecal
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
Max	maximum
MPS IIIA	Mucopolysaccharidosis Type IIIA
MRI	magnetic resonance imaging
n	Sample size
NCS	not clinically significant
PK	pharmacokinetic
Q2W	Every 2 weeks
Q4W	Every 4 weeks
rhHNS	Recombinant human heparan N-sulfatase

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
[redacted]	
$t_{1/2}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
TEAE	treatment-emergent adverse event
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
V_z/F	volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WHO	World Health Organization

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the planned statistical analyses for protocol SHP-610-201, a Phase IIb, 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. Shire is terminating this study early due to the insufficient evidence of efficacy for HGT-1410 in study HGT-SAN-093. An abbreviated clinical study report (aCSR) will be written for this study, as the study is not intended to contribute to the evaluation of product effectiveness or to provide definitive information on clinical pharmacology. This report will describe all the safety information included in a full report.

2.2 Background

Study SHP-610-201 is a Phase IIb, 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. Details of the study design, rationale, and procedures are documented in Protocol SHP-610-201.

2.3 Study Rationale

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 central nervous system 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.

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

3. STUDY OBJECTIVES

3.1 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.

3.2 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

3.3 Exploratory Objective

The exploratory objective of this study is to [redacted].

3.4 Pharmacokinetic and Pharmacodynamic Objectives

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

- The pharmacokinetics of HGT-1410 in serum, in all patients with PK assessment
- 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

3.5 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.

3.6 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.

4. STUDY DESIGN

4.1 General Description

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. 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 every 2 weeks (Q2W) and Group 2 will receive HGT-1410 every 4 weeks (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.

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.

4.2 Discussion of Study Design, Including the Choice of Control Group

This is an open-label extension study of Study HGT-SAN-093 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.

4.3 Method of Assigning Subjects to Treatment Group

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). 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.

4.4 Blinding

This study will not be blinded.

4.5 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.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 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

5.2 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

5.3 Exploratory Endpoint(s)

[redacted]

5.4 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.

5.5 Health Status Endpoint

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

5.6 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.

6. EFFICACY AND SAFETY VARIABLES

6.1 Schedule of Evaluations

Please refer to Protocol SHP-610-201 for the Schedule of Events tables for Group 1 [patients who received HGT-1410 Q2W in Study HGT-SAN-093], for Group 2 [patients who received HGT-1410 Q4W in Study HGT-SAN-093], 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], 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]).

6.2 Efficacy Assessments

6.2.1 Neurocognitive and Developmental Assessments

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of patient neurodevelopmental status (see Table 1). 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 (Bayley, 2005) 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 (Sparrow, 2005) 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 1.

Table 1 Neurodevelopmental Assessments Tests

Cognitive Test or Scale	Developmental or Cognitive Areas of Assessment
BSID-III	Summary score and sub-domains: - Cognitive - Motor - Social/Emotional - Language
KABC-II	Cognitive and processing skills
ADAPTIVE BEHAVIOR	
VABS-II	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

6.2.2 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.

6.2.3 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.

6.3 Magnetic Resonance Imaging

6.3.1 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.

6.3.2 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.

6.4 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 in Protocol SHP-610-201. 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 in Protocol SHP-610-201.

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.

6.5 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 in Protocol SHP-610-201.

6.6 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).

6.7 Safety Assessments

6.7.1 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 in Protocol SHP-610-201.

6.7.2 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 2, including the port and catheter track. Any abnormal change in findings will be recorded as an AE on the appropriate eCRF.

Table 2 Assessments for Physical Examinations

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

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.

6.7.3 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.

6.7.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing.

Clinical laboratory tests will include the laboratory tests presented for the HGT-SAN-093 CSR.

6.7.5 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 Protocol SHP-610-201, 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.

6.7.5.1 Standard CSF Safety Laboratory Assessments

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

6.7.5.2 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.

6.7.5.3 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, heparan sulfate (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 6.4.

6.7.5.4 [redacted]

[redacted]

6.7.6 Device Assessments

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

6.8 Adverse Events Assessments

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.

For a detailed definition on AEs, Serious AEs (SAEs), adverse events due to systemic exposure to HGT-1410, infusion/hypersensitivity reactions and management, IDDD-related adverse events, severity of AEs, and relatedness of AEs and SAEs, please refer to the SHP-610-201 Protocol Section 7.13.

7. STATISTICAL ANALYSIS

7.1 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 this SAP.

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.

Unless otherwise indicated, all summary statistics will be presented by treatment groups (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).

No summary statistics and hypothesis testing will be presented for efficacy data. Instead, subject listings will be presented for the selected efficacy endpoints.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis, for subjects who enrolled in SHP-610-201. 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.

7.2 Analysis Populations

The population for all 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 (SHP-610-201). 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.

7.3 Subject Disposition

The number of patients signed informed consent; 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. Subject disposition will also be presented in a listing.

7.4 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. Demographic data and baseline characteristics will be also presented in a listing.

7.5 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.

7.6 Medical History

Medical history will be coded using Medical Dictionary for Regulatory activities (MedDRA) Version 17.1 and provided as a listing.

7.7 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.

Duration of IT administration, summarized in weeks, is calculated by subtracting the date of first dose from date of last dose.

Duration of each IT administration (in minutes) 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.

The IT administration of study drug will be also presented in a listing.

7.8 Analysis of Efficacy

7.8.1 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 7.10.

7.8.2 Secondary Efficacy Analysis

7.8.2.1 Bayley Scales of Infant Development, Third Edition (BSID-III)/

The BSID-III data including developmental quotient (DQ), age equivalent scores, growth scores, total raw scores and scaled scores for each subtest (Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor) will be presented in a listing only.

The KABC-II is an alternative to BSID-III. Few subjects were administered KABC-II scale; however, these scores were considered invalid by the sites, hence no data for KABC-II will be presented.

7.8.2.2 Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

The VABS-II data including age equivalent scores, DQ, raw scores, and standard scores for each domain will be presented in a listing only.

7.8.2.3 Brain MRI

Although several MRI parameters will be captured, only the grey matter volume, the white matter volume, and the total intracranial CSF volume will be presented in a listing.

7.9 Analysis of Pharmacokinetic and Pharmacodynamic Data

7.9.1 Pharmacokinetic Measurement and Parameters

As study was closed earlier than planned, there were few PK samples collected and hence no analysis on pharmacokinetic measurement and parameters will be provided.

7.9.2 Pharmacodynamic Analyses

The levels of GAG (heparin sulfate) in CSF and urine (glycosaminoglycans/creatinine) are pharmacodynamic endpoints. The data for pharmacodynamic endpoints will be presented in a listing only, with the MRI data.

7.10 Analysis of Safety

7.10.1 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 earlier) in either HGT-SAN-093 or SHP-610-210 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 summarized by SOC and preferred term.

All treatment-emergent AEs, serious or life-threatening treatment-emergent AEs, treatment-emergent AEs leading to permanent discontinuation of study drug or resulting in death will be presented in a separate listing, respectively.

7.10.1.1 Investigational Product-Related AEs

Treatment-emergent AEs deemed by the investigator to be related (probably, possibly, or definitely related) to the investigational product (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.

7.10.1.2 IDDD and Surgical Procedure–Related AEs

Intrathecal drug delivery devices and procedure-related AEs will be summarized within 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.

7.10.2 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.

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. 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.

7.10.3 ECG Evaluations

A listing of clinically significant ECG findings, as assessed by the investigator will be provided.

7.10.4 Vital Signs

The IT-administration vital signs will be presented in a listing.

7.10.5 Anti-rhHNS Antibody in Serum and CSF

Anti-rhHNS antibody status (ie, positive or negative) at each assessment time from baseline will be presented in listings based on serum and CSF samples.

7.10.6 Concomitant Medications

Concomitant medications will be coded using the WHO DRUG Dictionary Enhanced December 2014. 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 presented in a listing.

7.10.7 Other Observations Related to Safety

7.10.7.1 IDDD Performance

The device failure/malfunction data will be presented in a listing only

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

8.1 Changes from the Analyses Planned in the Protocol

As Shire has decided to terminate this study early, and to summarize the study with an abbreviated CSR, not all dated collected in this study will be analyzed. Summary statistics will only be presented for baseline characteristics, exposure of study drug, and adverse events. The data of selected efficacy endpoints will be presented in listings only. All outputs will be presented for safety population and no efficacy population will be defined.

The following data will not be analyzed: health status (ITQoL) and pharmacokinetic assessments

However, SDTM data will be available for these endpoints.

9. REFERENCES

1. Bayley N. Bayley Scales of Infant and Toddler Development. 3 ed. San Antonio, TX The Psychological Corporation; 2005.

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

10. APPENDICES

10.1 APPENDIX II: List of Statistical Outputs

A list of statistical outputs is provided in the TFL shells.

10.2 APPENDIX III: Definitions and Programming Conventions

10.2.1 Calculation of DQ Scores

BSID-III: Divide the Age-equivalent score for cognitive domain (expressed in months) by the Age at Testing (expressed in months). Multiply the result by 100 to obtain percentages. These values will be provided by an outside vendor, Prophase.

VABS-II: First calculate the average age equivalent score by averaging out the age-equivalent scores for the following sub-domains – receptive, expressive, written, personal, domestic, community, interpersonal relationships, play and leisure time, coping skills. Divide the average Age-equivalent score (expressed in months) by the Age at Testing (expressed in months). Multiply the result by 100 to obtain percentages. NOTE: The average age-equivalent score (hence DQ) will be calculated based on the available items if at least two items have non-missing value. These values will be provided by an outside vendor, Prophase.

STATISTICAL ANALYSIS PLAN FOR INTERIM ANALYSIS

Protocol 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
Protocol Number:	SHP-610-201
Protocol Version/Date	Amendment 2 25 January 2017
Indication:	Long-term Treatment of Mucopolysaccharidosis Type IIIA (MPS IIIA or Sanfilippo Syndrome Type A)
Study Phase	IIb
SAP Author	[redacted], PhD; [redacted], PhD
SAP Analysis Type	Interim Analysis
SAP Version/Date	1.0 May 26, 2017

SHP-610-201 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES:

The planned statistical analyses are appropriate for the interim analysis of the SHP-610-201 data during the treatment period. These analyses are in accordance with the study objectives and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITIONS

1.1 Abbreviations

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration 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
BSID-III	Bayley Scales of Infant Development, Third Edition
CL/F	total body clearance for extravascular administration divided by the fraction of dose absorbed
C_{max}	maximum concentration occurring at t_{max}
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
DQ	developmental quotient
eCRF	electronic case report form
ECG	electrocardiogram
GAG	glycosaminoglycan
HGT	human genetic therapies
HS	heparan sulfate
IDDD	intrathecal drug delivery device
IT	intrathecal
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LP	lumbar puncture
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
Max	maximum
MPS IIIA	Mucopolysaccharidosis Type IIIA
MRI	magnetic resonance imaging
n	Sample size
NCS	not clinically significant
PK	pharmacokinetic
Q2W	Every 2 weeks
Q4W	Every 4 weeks
rhHNS	Recombinant human heparan N-sulfatase

Abbreviation	**Definition**
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
[redacted]	
$t_{1/2}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
TEAE	treatment-emergent adverse event
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
V_z/F	volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WHO	World Health Organization

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the planned interim analyses for protocol SHP-610-201 amendment 2, a Phase IIb, 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. Shire made a decision in August 2016 to terminate the Sanfilippo Syndrome Type A development program, including this extension study, due to the failure to meet the prespecified efficacy criteria in the pivotal Phase 2 study, HGT-SAN-093, and the resulting inability for the study to yield clinical proof-of-concept. After notification of early study termination, several investigators informed Shire that the IDDDs would remain implanted since in their opinion removal of devices would result in an increased risk to the patients. Therefore, this extension study (SHP-610-201) remains ongoing and has been extended to allow for safety follow-up of patients with partial or full devices still implanted after completion of the treatment period of the study. The statistical analyses and summary tabulations described in this interim SAP will provide the basis for the results sections of the abbreviated clinical study report (aCSR). An aCSR will be written to describe the results of the treatment period of the study, as the study is not intended to contribute to the evaluation of product effectiveness or to provide definitive information on clinical pharmacology. Full safety information will be reported.

2.2 Background

Study SHP-610-201 is a Phase IIb, 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. Details of the study design, rationale, and procedures are documented in Protocol SHP-610-201.

2.3 Study Rationale

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 central nervous system 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.

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

3. STUDY OBJECTIVES

3.1 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.

3.2 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

3.3 Exploratory Objective

The exploratory objective of this study is to [redacted]

3.4 Pharmacokinetic and Pharmacodynamic Objectives

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

- The pharmacokinetics of HGT-1410 in serum, in all patients with PK assessment
- 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

3.5 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.

3.6 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.

4. STUDY DESIGN

4.1 General Description

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. 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 every 2 weeks (Q2W) and Group 2 will receive HGT-1410 every 4 weeks (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.

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 or suture wing 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.

4.2 Discussion of Study Design, Including the Choice of Control Group

This is an open-label extension study of Study HGT-SAN-093 intended to provide ongoing treatment with HGT-1410 during the treatment period 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.

4.3 Method of Assigning Subjects to Treatment Group

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). 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.

4.4 Blinding

This study will not be blinded.

4.5 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.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 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

5.2 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

5.3 Exploratory Endpoint(s)

[redacted]

5.4 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.

5.5 Health Status Endpoint

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

5.6 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 treatment period of the study.

6. EFFICACY AND SAFETY VARIABLES

6.1 Schedule of Evaluations

Please refer to Protocol SHP-610-201 amendment 2 for the Schedule of Events tables for Group 1 (patients who received HGT-1410 Q2W in Study HGT-SAN-093), for Group 2 (patients who received HGT-1410 Q4W in Study HGT-SAN-093), 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), 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).

6.2 Efficacy Assessments

6.2.1 Neurocognitive and Developmental Assessments

The study methodology will include standardized neurodevelopmental assessments to provide a quantifiable measure of patient neurodevelopmental status (see Table 1). 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 (Bayley, 2005) 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 (Sparrow, 2005) 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 1.

Table 1 Neurodevelopmental Assessments Tests

Cognitive Test or Scale	Developmental or Cognitive Areas of Assessment
BSID-III	Summary score and sub-domains: - Cognitive - Motor - Social/Emotional - Language
KABC-II	Cognitive and processing skills
ADAPTIVE BEHAVIOR	
VABS-II	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

6.2.2 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.

6.2.3 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.

6.3 Magnetic Resonance Imaging

6.3.1 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.

6.3.2 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.

6.4 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 in Protocol SHP-610-201. 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 in Protocol SHP-610-201.

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.

6.5 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 in Protocol SHP-610-201.

6.6 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).

6.7 Safety Assessments

6.7.1 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 in Protocol SHP-610-201.

6.7.2 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 2, including the port and catheter track. Any abnormal change in findings will be recorded as an AE on the appropriate eCRF.

Table 2 Assessments for Physical Examinations

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

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.

6.7.3 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.

6.7.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing.

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 laboratory tests presented for the HGT-SAN-093 CSR.

6.7.5 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 Protocol SHP-610-201, 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.

6.7.5.1 Standard CSF Safety Laboratory Assessments

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

6.7.5.2 Anti-rhHNS Antibodies and Biomarkers in CSF and Serum

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.

Blood samples will be collected and evaluated at Shire or Shire-designated laboratories for the determination of serum anti-rhHNS antibodies.

6.7.5.3 CSF GAG Levels and Biomarkers

An aliquot of each CSF sample collected will be quick frozen for subsequent analysis of CSF GAG . The CSF pharmacodynamic sample will be obtained as described in protocol Section 7.11.5.3.

6.7.5.4 [redacted]

[redacted]

6.7.6 Device Assessments

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

6.8 Adverse Events Assessments

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.

For a detailed definition on AEs, Serious AEs (SAEs), adverse events due to systemic exposure to HGT-1410, infusion/hypersensitivity reactions and management, IDDD-related adverse events, severity of AEs, and relatedness of AEs and SAEs, please refer to the SHP-610-201 Protocol Section 7.13.

7. STATISTICAL ANALYSIS

7.1 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 this SAP.

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.

Unless otherwise indicated, all summary statistics will be presented by treatment groups (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).

No summary statistics and hypothesis testing will be presented for efficacy data. Instead, subject listings will be presented for the selected efficacy endpoints.

Data from Study HGT-SAN-093 will be combined with that of Study SHP-610-201 for analysis, for subjects who enrolled in SHP-610-201. 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.

7.2 Analysis Populations

The population for all 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 (SHP-610-201). 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.

7.3 Subject Disposition

The number of patients signed informed consent; the number and proportion of patients randomized, included in the safety population, completed the study, discontinued prematurely, completed the treatment period, and still in study will be presented in a summary table by treatment group; reasons for discontinuation/withdrawal will also be summarized. Subject disposition will also be presented in a listing.

7.4 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. Demographic data and baseline characteristics will be also presented in a listing.

7.5 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. Protocol violations will be defined as any major protocol deviation that affects study evaluations, such as a significant violation of admission (inclusion/exclusion) criteria. The protocol deviations will be presented in a listing and all protocol violations will be indicated by a flag.

7.6 Medical History

Medical history will be coded using Medical Dictionary for Regulatory activities (MedDRA) Version 17.1 and provided as a listing.

7.7 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.

Duration of IT administration, summarized in weeks, is calculated by subtracting the date of first dose from date of last dose.

Duration of each IT administration (in minutes) 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.

The IT administration of study drug will be also presented in a listing.

7.8 Analysis of Efficacy

7.8.1 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 7.10.

7.8.2 Secondary Efficacy Analysis

7.8.2.1 Bayley Scales of Infant Development, Third Edition (BSID-III)/

The BSID-III data including developmental quotient (DQ), age equivalent scores, growth scores, total raw scores and scaled scores for each subtest (Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor) will be presented in a listing only.

The KABC-II is an alternative to BSID-III. Few subjects were administered KABC-II scale; however, these scores were considered invalid by the sites, hence no data for KABC-II will be presented.

7.8.2.2 Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

The VABS-II data including age equivalent scores, DQ, raw scores, and standard scores for each domain will be presented in a listing only.

7.8.2.3 Brain MRI

Although several MRI parameters will be captured, only the grey matter volume, the white matter volume, and the total intracranial CSF volume will be presented in a listing.

7.9 Analysis of Pharmacokinetic and Pharmacodynamic Data

7.9.1 Pharmacokinetic Measurement and Parameters

As the treatment period of the study was closed earlier than planned, there were few PK samples collected and hence no analysis on pharmacokinetic measurement and parameters will be provided.

7.9.2 Pharmacodynamic Analyses

The levels of GAG (heparin sulfate) in CSF and urine (glycosaminoglycans/creatinine) are pharmacodynamic endpoints. The data for pharmacodynamic endpoints will be presented in a listing only, with the MRI data.

7.10 Analysis of Safety

7.10.1 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) version 17.1.

Treatment-emergent AEs, defined as all AEs from the time of initial IDDD implantation (or first dose if earlier) in either HGT-SAN-093 or SHP-610-201 to the data cut-off date, or 30 days after the date of last dose or 2 weeks after the date of device explant (whichever is later) if early termination, 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 summarized by SOC and preferred term.

All treatment-emergent AEs, serious or life-threatening treatment-emergent AEs, treatment-emergent AEs leading to permanent discontinuation of study drug or resulting in death will be presented in a separate listing, respectively.

7.10.1.1 Investigational Product-Related AEs

Treatment-emergent AEs deemed by the investigator to be related (probably, possibly, or definitely related) to the investigational product (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.

7.10.1.2 IDDD and Surgical Procedure–Related AEs

Intrathecal drug delivery devices and procedure-related AEs will be summarized within 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.

7.10.2 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.

Each laboratory result will be categorized as a patient having had (1) an abnormal and clinically significant (CS) value at any time between baseline and the data cut-off date, (2) no CS values at any time between baseline and the data cut-off date, but had at least 1 abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time between baseline and the data cut-off date. For any patient who experiences a CS laboratory result at any time between baseline and the data cut-off date 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.

7.10.3 ECG Evaluations

A listing of clinically significant ECG findings, as assessed by the investigator will be provided.

7.10.4 Vital Signs

The IT-administration vital signs will be presented in a listing.

7.10.5 Anti-rhHNS Antibody in Serum and CSF

Anti-rhHNS antibody status (ie, positive or negative) at each assessment time from baseline to the data cut-off date will be presented in listings based on serum and CSF samples.

7.10.6 Concomitant Medications, Therapies, and Medical/Surgical Interventions

All non-protocol treatments, including medications and over-the-counter medications, therapies/interventions administered to subjects, and medical/surgical procedures performed on the subjects that started on or after the reference date, which is the date of the IDDD implantation surgery or the first dose of HGT-1410 (whichever is earlier) in either HGT-SAN-093 or SHP-610-201, to the data cut-off date, or 30 days after the date of last dose or 2 weeks after the date of device explant (whichever is later) if early termination, are regarded as concomitant. Any medications/surgical procedures which ended before the reference date will be excluded; however, a medication/surgical procedure that started before the reference date and ended on or after the reference date will be included. The Concomitant medications will be coded using the WHO DRUG Dictionary Enhanced December 2014 and presented in a listing.

7.10.7 Other Observations Related to Safety

7.10.7.1 IDDD Performance

The device failure/malfunction data will be presented in a listing only for the subjects in the safety population with an IDDD implant.

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

8.1 Changes from the Analyses Planned in the Protocol

As this extension study will remain ongoing to allow for safety follow-up for patients with implanted devices (partial or full), despite the decision by Shire to terminate the development program, data for the treatment period of the study will be summarized in an abbreviated CSR. Not all data collected in this study will be analyzed. Summary statistics will only be presented for baseline characteristics, exposure of study drug, and adverse events. The data of selected efficacy endpoints will be presented in listings only. All outputs will be presented for safety population and no efficacy population will be defined. Information regarding the safety follow-up period will be analyzed after study completion and described in the final SAP.

The following data will not be analyzed: health status (ITQoL) and pharmacokinetic assessments.

However, SDTM data will be available for these endpoints.

9. REFERENCES

1. Bayley N. Bayley Scales of Infant and Toddler Development. 3 ed. San Antonio, TX The Psychological Corporation; 2005.

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

10. APPENDICES

10.1 APPENDIX II: List of Statistical Outputs

A list of statistical outputs is provided in the TFL shells.

10.2 APPENDIX III: Definitions and Programming Conventions

10.2.1 Calculation of DQ Scores

BSID-III: Divide the Age-equivalent score for cognitive domain (expressed in months) by the Age at Testing (expressed in months). Multiply the result by 100 to obtain percentages. These values will be provided by an outside vendor, Prophase.

VABS-II: First calculate the average age equivalent score by averaging out the age-equivalent scores for the following sub-domains – receptive, expressive, written, personal, domestic, community, interpersonal relationships, play and leisure time, coping skills. Divide the average Age-equivalent score (expressed in months) by the Age at Testing (expressed in months). Multiply the result by 100 to obtain percentages. NOTE: The average age-equivalent score (hence DQ) will be calculated based on the available items if at least two items have non-missing value. These values will be provided by an outside vendor, Prophase.

STATISTICAL ANALYSIS PLAN

ADDENDUM

FOR SAFETY FOLLOW-UP PERIOD

Protocol 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
Protocol Number:	SHP-610-201
Protocol Date:	25 January 2017 (Amendment 2)
Investigational Product:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410) SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire
SAP Author(s):	[redacted]
Release Date:	21 Jun 2019
Study Sponsor:	Shire 300 Shire Way Lexington, MA USA 02421
Shire Medical Monitor:	[redacted], DO

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1. ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
IDDD	intrathecal drug delivery device
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
IT	intrathecal
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class

2. RATIONALE FOR THE ADDENDUM

Study SHP-610-201 is a Phase IIb, open label extension of study HGT-SAN-093 evaluating the safety and efficacy of 45 mg HGT-1410 administered either every 2 weeks (Q2W) or every 4 weeks (Q4W) via an intrathecal drug delivery device (IDDD), versus no treatment, in subjects at a relatively early stage of mucopolysaccharidosis Type IIIA (MPS IIIA) disease. The study was designed 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. The statistical analysis plan (SAP) for interim analysis dated on 26 May 2017 provided a technical and detailed elaboration of the planned interim analysis based on the data with cut-off date of 28 June 2017 (treatment period) for protocol SHP-610-201 amendment 2.

During the treatment period, if a subject discontinued, or withdrew from the study, or the study was stopped by the sponsor, the IDDD was to be removed. If the investigator determined that the IDDD should not be removed (full or partial device) from the subject based upon a safety assessment, then the subject continued in the study under the safety follow-up period upon completion of their last treatment period visit. The safety follow-up period of study SHP-610-201 will monitor the safety of the device up to an additional 3 years or until the device is removed in the last subject.

As of 7 March 2019, Study SHP-610-201 is considered complete as the sponsor has determined that the safety follow-up period may be ended as no safety concerns have been raised and subjects will continue to be monitored by their physicians. This SAP addendum for the safety follow-up period provides the planned analysis on the safety of the device for the subjects who did not have the IDDD removed (full or partial) at the end of the treatment period, based on protocol SHP-610-201 Amendment 2, dated 25 January 2017.

3. GENERAL DESCRIPTION

If the Investigator determined that the device should not be removed from a subject based upon safety assessments at the end of treatment period, the device could remain in the subject (partial [catheter only] or full [port, catheter, and suture wings]) if the subject was doing clinically well and there were 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.

Subjects who did not have the IDDD removed (partial or full device) at the end of the treatment period of HGT-SAN-093 continued to be observed during a safety follow-up period with visits at the site every 6 months up to an additional 3 years until the IDDD has been fully explanted.

Determined by the sponsor to end the study, the global LPLV for the safety follow-up period was 7 March 2019 and this was the last visit of the study.

4. SAFETY VARIABLES

4.1 Schedule of Safety Evaluations

The schedule of safety evaluations of device was performed every 6 months (Refer to Appendix 5 of the study protocol [Amendment 2]).

4.2 Safety Endpoints

The safety endpoints for the safety follow-up period were:

- Symptom-directed PE
- Clinical laboratory tests (hematology, serum chemistry, urinalysis and standard CSF safety labs); only if indicated for a device-related AE
- X-ray (to check IDDD placement or for any device-related AEs)
- Concomitant medications, therapies, and procedures; only if indicated for a device-related AE
- Device-related AE monitoring
- Postoperative check of IDDD incision (postoperative evaluation can occur within 1-3 days after IDDD explantation)

5. STATISTICAL ANALYSIS

5.1 General Methodology

All statistical analyses will be performed using SAS® Version 9.3 or later.

Tabular summaries will be presented. Continuous variables will be summarized using descriptive statistics [sample size (N), mean, standard deviation (SD), minimum, median, and maximum]. Categorical variables will be summarized using the number and percentage.

For samples associated with multiple tests performed at the same visit (e.g. lab results), the latest valid result will be selected for analysis.

5.2 Analysis Populations

The safety population in safety follow-up period consists of subjects from HGT-SAN-093 whose IDDD was not removed (full or partial) at the end of the treatment period and agreed to participate in the safety follow-up period.

6. DATA DISPLAYS

6.1 Subject Disposition

The number of subjects who signed the informed consent for the safety follow-up period, are in the safety population for safety follow-up period, completed the safety follow-up period, and withdrawn from the safety follow-up period. Reasons for withdrawal will be provided.

Subject disposition will be presented in a by-subject listing.

6.2 Protocol Deviations

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

Protocol violations will be defined as any major protocol deviation that affects study evaluations during safety follow-up period. Subjects will be examined on a case-by-case basis prior to final database lock to determine whether conditions set forth in the study protocol have been violated.

The protocol deviations will be presented in a listing.

6.3 Demographics and Other Characteristics

Demographic and characteristics at the beginning of safety follow-up period, eg, age (years), gender (male, female), race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino) will be summarized for the safety population in the safety follow-up period. Age, in years, will be calculated by subtracting the date of birth from the date of informed consent for safety follow-up period plus 1 and dividing by 365.25 and then rounding down to two decimal places.

Demographic information will be presented in a by-subject listing.

6.4 Extent of Exposure

Duration of subjects/devices (weeks) in the safety follow-up period will be summarized.

The duration of the subject/device is calculated by subtracting the date of informed consent for safety follow-up period from the device removal date or end of safety follow-up period (whichever is earlier).

A listing for the duration of the device exposure will be presented by subject.

6.5 Safety Analysis

6.5.1 Adverse Events

Device-related AEs were recorded throughout the safety follow-up period. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 or higher.

AEs will be summarized descriptively. The summary will include the number and percentage of subjects with any AE, device surgical procedure related AE, device-related AE, any device-related serious AE (SAE), and any AE that lead to discontinuation.

AEs will be summarized by system organ class (SOC) and preferred term. The number and percentage of subjects experiencing an AE will be tabulated. Furthermore, AEs deemed as possibly/probably or definitely related to device surgical procedure, or IDDD will be summarized separately. SAEs and AEs which lead to study discontinuation will be similarly summarized.

By-subject listings will be provided for device-related AEs, device-related AEs resulting in death, SAEs, and AEs leading to discontinuation.

6.5.2 Laboratory Results

Clinical laboratory results will be presented only if indicated for a device-related AE during the safety follow-up period. By-subject listing of laboratory results will be provided.

6.5.3 Concomitant Medications, Therapies and Procedures

Concomitant medications, therapies and procedures will be reported only if indicated for a device-related AE, and will be coded using the WHO Drug Dictionary (Version 2009, Q4 or higher).

The concomitant medications, therapies and procedures that occur on or after the date of informed content for the safety follow-up period will be presented in a listing.