STATISTICAL ANALYSIS PLAN

NCT Number: NCT01299727

Study Title: An Open-Label Extension of Study HGT-SAN-055 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Administration of rhHNS in Patients with Sanfilippo Syndrome Type A (MPS IIIA)

Study Number: HGT-SAN-067

SAP Version and Date:

SAP Version 1.0: 31 October 2016
Amendment for Safety Follow-Up Period: 21 June 2019

STATISTICAL ANALYSIS PLAN

Protocol Title:	An Open-Label Extension of Study HGT-SAN-055 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Administration of rhHNS in Subjects with Sanfilippo Syndrome Type A (MPS IIIA)
Protocol Number:	HGT-SAN-067
Protocol Date:	08 February 2016 (Amendment 7)
Investigational Product:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
SAP Author(s):	[redacted], PhD
SAP Version:	1.0
Release Date:	31 October 2016
Study Sponsor:	Shire, Inc. 300 Shire Way Lexington, MA USA 02421
Shire Medical Monitor:	[redacted], DO

HGT-SAN-067 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES:

The planned statistical analyses are appropriate for the analysis of the HGT-SAN-067 data. These analyses are in accordance with the study objectives and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

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1 ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABR	auditory brainstem response
AE	adverse event
BSID-III	Bayley Scales of Infant Development, Third Edition
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
FDA	Food and Drug Administration
FPSS/TDS	Four Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
HS	heparan sulfate
ICH	International Conference on Harmonization
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
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
QoL	quality of life
Q4W	once per month
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP	Statistical Analysis Plan
Shire HGT	Shire Human Genetic Therapies, Inc.
US	United States
VABS-II	Vineland Adaptive Behavior Scales

2 INTRODUCTION

2.1 Background

This study, HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. The study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of intrathecal (IT) administration of 3 dose levels (10 , 45 , and 90 mg once per month [Q4W]) of recombinant human heparan N-sulfatase (rhHNS, HGT-1410) via an intrathecal drug delivery device (IDDD) in subjects with Sanfilippo Syndrome Type A (MPS IIIA) who successfully complete the Phase I/II study HGT-SAN-055 (including end of study [EOS] assessments) and elect to continue to receive HGT-1410 treatment.

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the planned statistical analyses for protocol HGT-SAN-067. Populations for analyses, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR).

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

This SAP is based on protocol HGT-SAN-067 Amendment 7, dated 08 February 2016. The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study and the operational aspects of clinical assessments and timing for completing a subject in this study

2.2 Study Rationale

This extension study (Study HGT-SAN-067) will evaluate the effects of long-term HGT-1410 administration on safety, clinical activity, and biomarker outcomes in subjects who completed Study HGT-SAN-055 and elected to continue therapy with HGT-1410.

3 STUDY OBJECTIVES

3.1 Primary Objective

- To collect long-term safety and tolerability data in subjects with Sanfilippo Syndrome Type A (MPS IIIA) who received HGT-1410 via a surgically implanted IDDD in study HGT-SAN-055 and elect to continue therapy in study HGT-SAN-067.

3.2 Secondary Objectives

The secondary objectives of this study are to:

- To collect, as measures of drug efficacy, over an extended treatment period (as change from baseline), the following: clinical, neurological, cognitive, behavioral, functional, and quality of life (QoL) assessments, together with potential imaging and biochemical biomarkers.

3.3 Exploratory Objective

- [redacted]

4 STUDY DESIGN

4.1 General Description

Study HGT-SAN-055 was a multicenter, multiple-dose, dose escalation study designed to evaluate the safety, tolerability, and clinical activity of up to 3 dose levels ([10, 45, and 90 mg] monthly for 6 months) of rhHNS administered via an IDDD in subjects with MPS IIIA. The study was planned to enroll up to 15 subjects to ensure a total of 12 subjects who completed the study (4 subjects per dose group). The primary objective was to determine the safety and tolerability of rhHNS via ascending doses administered via a surgically implanted IDDD once monthly for 6 months, in subjects with MPS IIIA. Safety was assessed through adverse events (AEs; types and severity), changes in clinical laboratory tests (serum chemistry, hematology and urinalysis), electrocardiograms (ECGs), cerebrospinal fluid (CSF) chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (CSF and serum). Secondary endpoints include the determination of the concentration of rhHNS in CSF and serum, and changes in CSF biomarkers. Additional secondary endpoints of potential efficacy included neurocognitive and developmental testing, quality of life measurements, and neurological assessments.

Long-term safety, clinical activity and biomarker outcomes of IT administration of rhHNS have been evaluated through the extension study, HGT-SAN-067. Subjects continued in the same treatment group they were assigned to in the HGT-SAN-055 study, with the exception of subjects in the 10 mg group who started transitioning in July 2013 to the 45 mg group following Protocol Amendment 4 (dated 03 May 2013). For all analyses under this SAP, subjects will be presented under the original treatment arm assigned in HGT-SAN-055. Analyses will be conducted on combined data from HGT-SAN-055 and HGT-SAN-067. In order to maintain a nomenclature system based on study chronology across the original HGT SAN-055 study and this extension study, the Baseline Visit for this extension study will be considered to be the day the subject received their first IT dose of HGT-1410 in Study HGT SAN 055.

The HGT-SAN-055 EOS assessment information provided the screening/start of study information for subjects who continued into the HGT-SAN-067 extension study. Once eligibility was confirmed, informed consent must have been obtained anytime from Week 20 in HGT-SAN-055 prior to performing any study-related procedures that were specific to HGT-SAN-067. This allowed subjects to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT SAN-067.

Enrolled subjects checked in to the study center 1 day before each of the scheduled HGT-1410 dosing days for safety assessments (designated Day 1). If no safety concerns existed, the subject subsequently received IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there were no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may have been combined and performed on Day 2; if this was done the results were to be recorded as Day 2. Subjects were to remain in the study center for at least 4 hours following dosing with HGT-1410 and were discharged from the unit when deemed clinically stable by the Investigator.

All subjects were to receive a series of standardized neurodevelopment assessments in the HGT-SAN-055 study. These assessments were to occur at Baseline and either prior to or at the 6-month time point. Subjects were to continue in HGT-SAN-067 with whichever age specific assessment they began in HGT-SAN-055. If, however, a subject's capability improves and they became capable of completing assessments at a higher level, such additional assessments may have been added. Any additional assessments were to be performed after the original assessments (those previously used in study HGT SAN-055) had been carried out. A magnetic resonance imaging (MRI) of the head and auditory brainstem response (ABR) testing were performed at Months 12, 24, 36, 54, 60, 72, 84, 96, 102 and EOS (only for MRI). X-rays may have been performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy should have been employed intraoperatively to guide catheter placement. Thus, subjects may have undergone 3 X ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. Since the number of IDDD revisions/replacements was limited to 2 in any 6 month period (including the time in the HGT-SAN-055 study), the number of protocol associated X-ray evaluations was limited to 6 exposures in any 6 month period (including time in the HGT-SAN-055). Subjects were also to have X-ray examinations of the device performed at the EOS visit if the subject was to continue to receive intrathecal HGT-1410 beyond the end of the study.

Subjects were evaluated for safety throughout the study. Use of concomitant medications, therapies, and procedures were recorded and AEs were monitored. Adverse events that occurred in HGT SAN-055 and that were ongoing at enrollment in HGT-SAN-067 were to be captured in the case report forms (CRFs) for study HGT-SAN-067. For these ongoing AEs, the records from HGT-SAN-067 were reported and the records from HGT-SAN-055 were to be excluded. Specific safety stopping criteria were applied and were based on the types and severity of AEs reported while on study. These data were reviewed to inform the decision to discontinue a subject, a dose group, or the study as a whole.

All subjects were to have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 102); however, this extension study was discontinued early as efficacy criteria were not met in the Phase IIb safety and efficacy study, HGT-SAN-093, and the study did not yield clinical proof-of-concept and all studies in the Sanfilippo Syndrome Type A program have been discontinued. The EOS procedures included standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, ABR, child health questionnaires, MRI and an X-ray examination of the device.

All subjects were to be contacted by telephone or have a visit for a Final Safety Follow up, to be conducted at 30 (±7) days after the EOS visit to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD would be used to obtain CSF samples and to deliver administrations of HGT-1410. However, if a subject's IDDD appeared nonfunctional or if its use was precluded on a scheduled day of dosing, site personnel were to refer to the operations manual (for the PORT-A-CATH IDDD) or the IDDD Manual (for the SOPH-A-PORT Mini S

IDDD), which describes the investigation and management of IDDD-related issues. This included possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements could occur in any 6-month period. If revision or replacement of the IDDD could not be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the subject experienced more than 2 IDDD malfunctions in a 6-month period (including participation in study HGT-SAN-055), HGT-1410 was to be administered via lumbar puncture (LP). Study drug may have been administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must have occurred.

If there was no significant safety risk in the opinion of the Investigator, a non-functional IDDD may have been left in situ for up to 3 months.

In light of the higher than expected complications experienced with the PORT-A-CATH IDDD, the SOPH-A-PORT Mini S device was introduced for those subjects requiring replacement or revision. This device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments were included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

Subjects who discontinued or were withdrawn before receiving 3 monthly IT injections were not have to have undergone the EOS evaluations but were to have their IDDD removed.

In the protocol, it was planned that subjects were to have the IDDD removed when they discontinued from the study, unless the subject was continuing to receive treatment through another mechanism (eg, extension study, expanded access, commercially available). However, during study close out after the study was discontinued early, it was determined that some investigators would prefer to not remove the IDDD for some subjects unless a safety concern arises.

4.2 Discussion for Study Design, Including the Choice of Control Groups

This is an open-label, non-randomized study; all subjects enrolled in this study will be treated with HGT-1410. Subjects will initially receive the same dose of HGT-1410 they received in Study HGT-SAN-055.

4.3 Method of Assigning Subjects to Treatment Groups

All subjects enrolled in this extension study initially received doses of HGT-1410 Q4W via an IDDD at the same dose (10, 45, and 90 mg) as the group to which they were assigned in Study HGT-SAN-055:

- Group 1: HGT-1410 administered by IT injection 10 mg once per month (Q4W)
- Group 2: HGT-1410 administered by IT injection 45 mg once per month (Q4W)
- Group 3: HGT-1410 administered by IT injection 90 mg once per month (Q4W)

Subjects assigned to Group 1 had their dose increased to 45 mg Q4W at the first administration of HGT-1410 following full approval of Protocol Amendment 4.

4.4 Blinding

There was no blinding to study drug as this is an open-label study.

4.5 Randomization

There was no randomization to treatment in this study.

4.6 Determination of Sample Size

Since this was an extension study, sample size was determined by the number of subjects who completed HGT-SAN-055 (maximum of 12 subjects) and elected to continue treatment with HGT-1410 in this study. Hence no statistical estimation of the sample size was performed.

5 EFFICACY AND SAFETY VARIABLES

5.1 Schedule of Evaluations

The schedule of evaluations can be found in Section 9.4 of this SAP, which can also be found in Appendices 1 of the study protocol (Amendment 7).

5.2 Primary Endpoints

The primary endpoints of this study were related to the long-term safety of intrathecal HGT-1410 administration. The safety endpoints were:

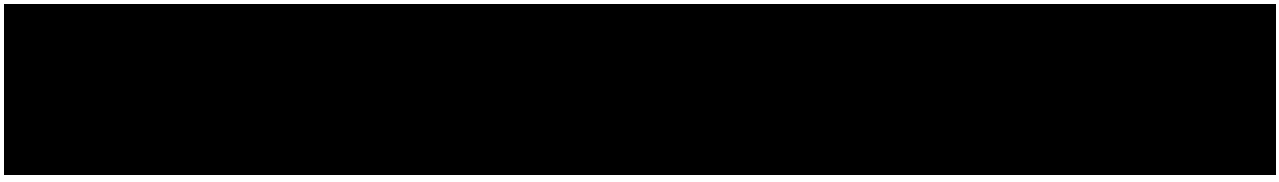
- AEs (type and severity)
- changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis)
- electrocardiograms (ECG)
- CSF chemistries (including cell counts and inflammatory markers)
- anti-rhHNS antibodies (in CSF and serum).

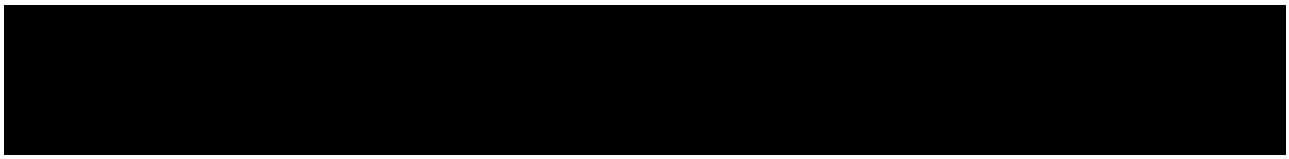
5.3 Secondary Endpoints

The secondary endpoints of this study were to collect over an extended treatment period (as the change from baseline [defined as the start of the HGT-SAN-055 study]) clinical and potential surrogate biomarker efficacy data:

- Measures of standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, QoL questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate (HS) and HS derivatives in CSF and glycosaminoglycan (GAG), including HS and HS derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), (also known as Brainstem Auditory Evoked Potentials).

5.4 SOPH-A-PORT Mini S Assessments





6 STATISTICAL ANALYSIS

6.1 General Methodology

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

Tabular summaries will be presented by rhHNS dose group (10, 45, and 90 mg). 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 in each category. Graphical techniques will also be used to assess trends across time per treatment group. In particular, spaghetti plots to help visualize the trajectories or time trends of individual subjects within the same plot will be used. For all analyses, baseline will be the measurement from the day the subject received their first IT dose of HGT-1410 in Study HGT SAN 055. Results (e.g., mean, SD) from all visits will be displayed with significant digits consistent with the measured precision of the test or original value.

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

6.2 Analysis Populations

The safety population is the only analysis population in this study. The safety population will consist of all eligible subjects from HGT-SAN-055 who have agreed to participate in the extension study, HGT-SAN-067. This population will be used to perform both safety and efficacy analyses.

6.3 Handling of Missing Data

If data at the baseline visit are not available, then the most recent available pre-treatment visit 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.

7 Data Displays

Tabular summaries will be presented by rhHNS dose group (10 mg, 45 mg, 90 mg). Data listings will be presented for every dataset described under this section. Data listings will be sorted by rhHNS dose group, rhHNS dose, site number, and subject number.

7.1 Subject Disposition

The number of subjects who signed the informed consent, are in the safety population, completed the study, withdrawn from the study, and transitioned from 10 to 45 mg will be reported. Reasons for withdrawal will be tabulated.

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

7.2 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, such as a significant violation of admission (inclusion/exclusion) criteria. 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. If applicable, the determination of protocol violations will be performed by the Shire Human Genetic Therapies, Inc. (Shire HGT) Medical Monitor in consultation with the Study Biostatistician.

The protocol deviations will be presented in a listing and all protocol violations will be indicated by a flag.

7.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, 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), ethnicity (Hispanic or Latino, Not Hispanic or Latino), weight (kg), height (cm) and head circumference (cm) will be summarized. Age, in years, will be calculated by subtracting the date of birth from the date of informed consent 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.

7.4 Medical History

A listing of medical and surgical histories will be provided for each subject.

7.5 Treatment Compliance and Extent of Exposure

Drug administration information will be presented by summarizing the duration of study drug exposure (weeks), the actual average dose (mg) and the number of infusions received.

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

By-subject listings of lot numbers of rhHNS received will be presented. A listing for drug administration including duration of administration will be presented by subject.

7.6 Analysis of Clinical Endpoints

7.6.1 Bayley Scales of Infant Development III (BSID-III)

The Bayley Scales of Infant Development is a standard series of measurements used primarily to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers, ages 0-42 months. This measure consists of a series of developmental play tasks and takes between 45 - 60 minutes to administer. Raw scores of successfully completed items will be converted to developmental age equivalent scores as well as composite scores, by referring to appropriate conversion tables in the BSID-III manual (Bayley, 2006). The mean composite score is 100 and the standard deviation (SD) is 15. Developmental Quotients (DQ) will be computed as a ratio, expressed as a percentage using the age equivalent score divided by the age at testing (i.e., [age equivalent score/chronological age] x 100).

Note that the determination of whether a subject received BSID-III or KABC-II at a particular assessment time was made based on an algorithm that includes the subject's calendar age and corresponding VABS-II age equivalent score. When the Bayley is used, the age equivalent scores and DQ scores for each subtest i.e. Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor will be summarized at each assessment time point. The corresponding change from baseline at visits will be summarized as well. BSID-III data will be presented in a by-subject listing.

7.6.2 Kaufman Assessment Battery for Children II (KABC-II)

The Kaufman Assessment Battery for Children is an individually administered measure of the processing and reasoning abilities of children and adolescents between the ages of three and eighteen years. A detailed description of the KABC-II is provided in the KABC-II manual (Kaufman, 2004).

The KABC-II is an alternative to BSID-III. The KABC-II DQ scores, which are based on the average non-verbal age equivalent scores (see appendix I for additional details) will be combined with the BSID-III cognitive DQ scores and summarized at each assessment time point. The change from baseline at visits will be summarized as well. Similarly, the corresponding age-equivalent scores will be tabulated. Most of the subjects will have either only BSID-III data or KABC-II data. If a subject 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. KABC-II data will be presented in by-subject listings (3-6 years and 7-18 years).

Plots of mean BSID-III/KABC-II DQ scores across time will be presented. A spaghetti plot of DQ scores (and corresponding age-equivalent scores) of BSID-III/KABS-II against chronological age will be presented. On the graph the time when 10 mg subject switched to 45 mg will be indicated.

7.6.3 Vineland Adaptive Behavior Scales II (VABS-II)

The Vineland Adaptive Behavior Scales test measures adaptive behaviors, including the ability to cope with environmental changes, to learn new everyday skills, and to demonstrate independence. It is an instrument that supports the diagnosis of intellectual and developmental disabilities in subjects aged birth to 90 years. This test measures 5 key domains: communication, daily living skills, socialization, motor skills, and the adaptive behavior composite (a composite of the other four domains). The raw scores will be converted to domain standard scores (mean 100, SD 15) and domain-specific age equivalents, by referring to the appropriate conversion tables in the VABS-II manual (Sparrow, 2005). Tabular summaries of the age equivalent and DQ for each subdomain (expressive, written, personal, domestic, community, interpersonal relationships, play and leisure time, coping skills, gross, and fine) and the standard scores for domains, and the corresponding change from baseline will be presented at each assessment time point from baseline. VABS-II data will be presented in a by-subject listing.

A spaghetti plot of mean age equivalent score against chronological age will be presented. On the graph the time when 10 mg subject switched to 45 mg will be indicated.

7.6.4 Four Point Scoring System (FPSS)

The FPSS is a Sanfillipo Syndrome -specific disability assessment, developed by Meyer et al (Meyer, 2007) which assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. A score of 3 points is assigned for normal function, 2 points for beginning of regression, 1 point for severe level of regression, and 0 points for lost skills. The total disability score (TDS) is the average of the motor function, speech, and cognitive function scores.

Tabular summaries of the FPSS domain scores and the TDS will be presented at each assessment time point. The corresponding change from baseline will be summarized as well. FPSS data will be presented in a by-subject listing.

7.7 Analysis of Biochemical Endpoints

7.7.1 Total Heparan Sulfate Levels

The observed values at each visit and the change from baseline to each of the post-baseline visits will be descriptively summarized for CSF total heparin sulfate levels by dose group. Heparin sulfate levels (CSF) will be presented in a by-subject listing.

Graphical plot of mean CSF total HS levels across time will be presented. In addition, a spaghetti plot of total heparin sulfate levels over time will be presented. The impact of positive serum anti-rhHNS antibody result will also be explored graphically using a spaghetti plot and/or individual subject plots. Urine GAG levels will be presented in a by-subject listing.

7.8 Analysis of Imaging Endpoints

7.8.1 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 at each visit and changes from baseline to each of the post-baseline visits will be descriptively summarized for these MRI parameters by dose group. Brain MRI data will be presented in a by-subject listing.

A spaghetti plots of MRI parameters against chronological age will be presented.

7.9 Safety Analysis

The safety parameters include: AEs, ECG, standard hematology, serum chemistry, urinalysis, CSF standard chemistry, and anti-rhHNS antibody.

7.9.1 Adverse Events

Aes will be recorded throughout the study and at early termination. Aes will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 or higher.

Treatment-emergent Aes, defined as all Aes from the time of the surgery for first IDDD implantation in HGT-SAN-055 to the last day of reporting period (or cut-off date), will be summarized by treatment group. The summary will include the number and percentage of subjects with any AE, any drug-related AE, any surgery-related AE, any IDDD-related AE, any IT administration process-related AE, any severe AE, any serious AE (SAE), any serious drug related AE, and any AE that lead to discontinuation.

Treatment emergent Aes will be summarized by system organ class (SOC) and preferred term by dose group. The number and percentage of subjects experiencing an AE will be tabulated; recurrent Aes observed within a subject will be counted once. Furthermore, treatment-emergent Aes deemed as possibly/probably or definitely related to device surgical procedure, IDDD, investigational product, and IT administration process will be summarized separately. Treatment-emergent SAEs and treatment-emergent Aes which lead to study discontinuation will be similarly summarized.

By-subject listings will be provided for treatment-emergent Aes, treatment-emergent SAEs, deaths, and treatment-emergent Aes leading to discontinuation.

In general, an AE will be considered a treatment emergent AE if it cannot be definitively categorized by the available components (day, month, year) of the AE onset date with respect to the date of the IDDD implantation.

7.9.2 Laboratory Results

The observed value and change from baseline to the end of reporting period for serum chemistry, hematology and urinalysis will be summarized by dose group. The shift in observed value with

respect to normal range between baseline and end of reporting period will also be summarized for serum chemistry, hematology, and urinalysis data.

By-subject listings of laboratory results (serum chemistry, hematology, and urinalysis) will be provided for baseline and the end of the reporting period. Listings will also be provided for clinically significant laboratory values at any time post-baseline that were not considered clinically significant at Baseline.

7.9.3 **CSF Standard Chemistries**

The CSF standard chemistries will be analyzed in a manner similar to that described in Section 7.9.2.

A by-subject listing of CSF standard chemistries at baseline and the end of the reporting period will be provided. Clinically significant CSF laboratory values at any time post-baseline that were not considered clinically significant at Baseline will also be listed by subject.

7.9.4 **Anti-rhHNS Antibody Assay Results**

Anti-rhHNS antibodies in serum and CSF will be monitored throughout the study. Antibody status (i.e. positive or negative) at each assessment time will be summarized in terms of counts and proportion. A plot of serum antibody titer of each subject with a positive status at least one visit, over time, will be presented by dose group.

Listings of anti-rhHNS antibody results, based on serum samples and CSF samples, will be provided by subject.

7.9.5 **12-lead Electrocardiogram (ECG)**

The ECG data will be presented in terms of listings only.

7.9.6 **Vital Signs**

There are two types of vital sign assessments: IT administration and non-IT administration vital signs. Vital signs assessments will include temperature [c], pulse [bpm], blood pressure (systolic and diastolic) [mmHg], and respiration [bpm]. The non-IT administration vital signs will be measured at several times before and after the treatment start. Vital sign data will be presented as a listing only.

7.9.1 **Concomitant Medications**

Concomitant medications will be coded using the WHO Drug Dictionary (Version 2009, Q4 or higher).

The concomitant medications that occur from the time of surgery for IDDD implantation until the safety follow-up visit (or 30 days from the EOS visit) will be presented as a listing only.

7.9.2 **IDDD Exposure and Failures**

IDDD Exposure and Failures will be presented as a listing only for the subjects in the safety population with IDDD Implant.

7.10 Analysis of Pharmacokinetic Data

Pharmacokinetic assessments were not included in HGT-SAN-067, and therefore no pharmacokinetic analysis will be performed in this study.

8 CHANGES IN THE PLANNED ANALYSES

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, including the data for:

- Auditory Brainstem Response (ABR) (Secondary Endpoint)
- Children's Sleep Habits Rating Scale (Secondary Endpoint)
- Movement Assessment Battery for Children II (MABC-II)
- Child Health Questionnaire-50
- Child Health Questionnaire-87
- Infant Toddler QOL Questionnaire – 97 (Secondary Endpoint)
- Sanfilippo Behavior rating Scale (SBRS)
- Concomitant Therapies, and Procedures
- IDDD analysis

However, SDTM data will be available for these endpoints.

9 REFERENCES

1. Bayley N. Bayley Scales of Infant and Toddler Development– Third Edition. San Antonio, TX: Harcourt Assessment Inc., 2006

2. Kaufman AS, Kaufman NL. Manual for the Kaufman Assessment Battery for Children: Second Edition (KABC-II). Circle Pines, MN: AGS Publishing, 2004C

3. Sparrow, Sara S., Domenic V. Cicchetti, and David A. Balla. Vineland Adaptive Behavior Scales, Second Edition. Minneapolis, MN: Pearson Assessments, 2005.

4. Meyer A, Kossow K, Gal A, et al. Scoring evaluation of the natural course of mucopolysaccharidosis type IIIA (Sanfilippo syndrome type A). Pediatrics 2007;120:e1255 61.

10 Appendices

10.1 Appendix I – 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.

KABC-II (Age at testing 3 – 6 yrs): First calculate the average Non-verbal age equivalent score by averaging out the age-equivalent scores for the following items – Conceptual Thinking, face recognition, story completion, triangles, pattern reasoning, hand movements. Divide the average non-verbal 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.

KABC-II (Age at testing 7 – 18 yrs): First calculate the average Non-verbal age equivalent score by averaging out the age-equivalent scores for the following items – story completion, triangles, block counting, pattern reasoning, hand movements. Divide the average non-verbal 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.

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STATISTICAL ANALYSIS PLAN

ADDENDUM

FOR SAFETY FOLLOW-UP PERIOD

Protocol Title:	An Open-Label Extension of Study HGT-SAN-055 Evaluating Long-Term Safety and Clinical Outcomes of Intrathecal Administration of rhHNS in Subjects with Sanfilippo Syndrome Type A (MPS IIIA)
Protocol Number:	HGT-SAN-067
Protocol Date:	01 February 2017 (Amendment 8)
Investigational Product:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
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
EOS	end of study
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 HGT-SAN-067 is an open-label, long term, multicenter, extension of Study HGT-SAN-055. The study was designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of intrathecal (IT) administration of 3 dose levels (10 , 45 , and 90 mg once per month [Q4W]) of recombinant human heparan N-sulfatase (rhHNS, HGT-1410) via an intrathecal drug delivery device (IDDD) in subjects with Sanfilippo Syndrome Type A (MPS IIIA) who successfully complete the Phase I/II study HGT-SAN-055 (including end of study [EOS] assessments) and elect to continue to receive HGT-1410 treatment. The statistical analysis plan (SAP) for interim analysis dated on 24 March 2017 provided a technical and detailed elaboration of the planned interim analysis based on the data with cut-off date of 30th January 2017 (treatment period) for protocol HGT-SAN-067 amendment 8.

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 HGT-SAN-067 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 28 February 2019, Study HGT-SAN-067 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 HGT-SAN-067 Amendment 8, dated 01 February 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-067 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 28 February 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 1 of the study protocol [Amendment 8]).

4.2 Safety Endpoints

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

- 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 AEs

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-067 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.