CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Original Protocol: 21 June 2010
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Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter
Sponsor:	Shire
Medical Monitor:	[redacted], MD [redacted] Shire Human Genetic Therapies, Inc. 700 Main Street Cambridge, MA 02139, USA Telephone: [redacted] Fax: [redacted] (USA)

	Date
Original Protocol:	21 June 2010

Confidentiality Statement

SYNOPSIS

Sponsor:

Shire

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS)

Name of Active Ingredient:

rhHNS

Name of Inactive Ingredient:

N/A

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

Study Phase: I/II

Primary Objective:

To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received rhHNS via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy.

Secondary Objectives:

To collect as indications 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.

Study Endpoints:

The primary endpoint of this study is:

To determine the long-term safety of intrathecal rhHNS administration, as measured by adverse events (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms, cerebrospinal fluid (CSF) chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in cerebrospinal fluid (CSF) and serum.
- Concentration of inflammatory cytokines in serum and CSF.

- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and CSF
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), aka Brainstem Auditory Evoked Potentials.

Study Design:

This is a multicenter, multiple-dose, open-label extension of Study HGT-SAN-055 designed to evaluate the long-term safety and clinical activity and biomarker outcomes of intrathecal administration of 3 dose levels (10 mg and 45 mg once per month and 45 mg every other week [EOW]) of rhHNS via an IDDD in patients with MPS IIIA.

Patients will continue in the treatment group as they participated in the HGT-SAN-055 study:

- Group 1: rhHNS administered by IT injection 10 mg once per month for a total of 6 months
- Group 2: rhHNS administered by IT injection 45 mg once per month for a total of 6 months
- Group 3: rhHNS administered by IT injection 45 mg EOW for a total of 6 months

It is anticipated that all patients successfully completing the HGT-SAN-055 study will elect to continue to receive intrathecal (IT) rhHNS per their previous schedule in Study HGT-SAN-055 by consenting to participate, without interruption, in the HGT-SAN-067 extension study. Thus, for nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055.

Patients whose parents/legal guardians provide written informed consent/assent to participate in this study will check in with the study center 1 day prior to rhHNS dosing for safety assessments on each rhHNS treatment week. If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2. Patients will be discharged from the inpatient unit a minimum of 1 day following dosing with rhHNS and when deemed clinically stable by the Investigator. The patient will have already received a standardized battery of neurodevelopmental assessments at the baseline and 6 month time points in the HGT-SAN-055 study. These same assessments and tests will also be performed at 12, 24, 36, and 48 months. Similarly, MRI of the head, ABR testing, CSF sampling via lumbar puncture and any other procedures requiring anesthesia will be performed at 12, 24, 36, and 48 months.

All patients will undergo end of study procedures 30 (±7) days following their last administration of rhHNS. End of study (EOS) procedures will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, ABR, and MRI.

All patients will be contacted by telephone for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS procedures to collect updated information on adverse events and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all administrations of rhHNS. However, if a patient's IDDD becomes nonfunctional or infected, it will be replaced so that the patient can remain on the study.

If use of the IDDD is precluded on a scheduled day of dosing, the IDDD will be declared a failure; no study drug will be administered, nor CSF sample obtained on that visit. Unlike the HGT-SAN-055 study, no study drug will be administered by lumbar puncture in this extension study. Upon declaration of failure, the IDDD will be removed and the patient scheduled for re-implantation of a new IDDD at the earliest convenience, so that the patient may remain on, or remain as close as possible, to his/her original IT rhHNS dosing schedule. Note: Patients will require 1 week of recovery time from time of re-implantation, during which time the IDDD cannot be used, this may result in a delay in the next scheduled dose of rhHNS. The patient will resume his or her original dosing schedule; no catch-up dosing will occur.

If a patient discontinues or is withdrawn from the study or the study is stopped by the Sponsor, the IDDD will be removed as part of the End of Study Procedures.

Study Population:

A maximum of twelve patients are planned for this study. To be eligible for participation, patients will have completed all study requirements in Study HGT-SAN-055 and will have elected to continue treatment with rhHNS.

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

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

1. Patients must have completed all study requirements and assessments for Study HGT-SAN-055 prior to enrolling in this extension study and must have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board / Independent Ethics Committee-approved informed consent form after all relevant aspects of the study have been explained and discussed with the patient. The guardians' consent and patient's assent, as relevant, must be obtained.
3. The patient has received and tolerated treatment with rhHNS, completed the End of Study visit, and has received at least 80% of the total planned infusions within the last 6 months in study HGT-SAN-055, (ie, at least 5/6 ([Group 1 or 2] or 10/12 infusions [Group 3]).
4. Patients must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or at anytime during the study:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.

3. The patient has significant non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has significant MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a female patient of childbearing potential, who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA or used any other intrathecal delivery device other than what was used in Study HGT-SAN-055, within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.
12. The patient's parent(s), or patient's legal guardian(s) is/are unable to provide consent or the patient cannot provide assent, as appropriate, due to, but not limited to, the inability to understand the nature, scope, and possible consequences of the study, or do/does not agree to comply with the protocol defined schedule of assessments.

Test Product; Dose; and Mode of Administration:
Recombinant human heparan N-sulfatase (rhHNS) will be administered via an IDDD according to the same dosing regimen to which the patient was assigned in HGT-SAN-055 (ie, 10 mg monthly, 45 mg monthly, or 45 mg EOW).

Reference Therapy; Dose; and Mode of Administration: Not Applicable

Duration of Treatment:

The study duration will be a maximum duration of 4 years of rhHNS treatment or until rhHNS is commercially available, the patient discontinues from the study, the Sponsor stops the study, or the Sponsor discontinues the development of rhHNS. Study completion will be defined as the time at which a patient completes 4 years of rhHNS treatment (including participation in study HGT-SAN-055), or transitions to commercially available rhHNS or discontinues from this study for other reasons.

Pharmacokinetic Variables:

Pharmacokinetics will not be assessed in this study.

Safety Assessments:
Safety evaluations will include vital signs, physical examinations, adverse event (AE) assessments, and electrocardiograms (ECG); serum chemistry, hematology, and urine laboratory tests; and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods:
The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time which may be attributed to treatment. For continuous data, 95% confidence interval around the mean will be presented.

The analysis population consists of all eligible patients from HGT-SAN-055, who have agreed to participate in the extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Most Recent Protocol Amendment (if applicable): N/A

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABR	Auditory Brainstem Response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CNS	central nervous system
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CO_2	carbon dioxide
CRO	contract research organization
CSF	cerebrospinal fluid
DDD	drug delivery device
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
FDA	Food and Drug Administration
FG	formylglycine

FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonisation
ICP	intracranial pressure
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgE	immunoglobulin E
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MABC-2	Movement Assessment Battery for Children, Second Edition

MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
QoL	quality of life
PE	pressure-equalization
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)
WHODRL	World Health Organization Drug Reference List

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. The patient's treatment group, dosing regimen, and the intrathecal drug delivery device (IDDD) will be the same as that employed in study HGT-SAN-055.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is a lysosomal storage disease (LSD) caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. MPS IIIA results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtypes A and B similar in prevalence, accounting for approximately 90% of all cases of MPS III.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1, 2,3] In summary, there is widespread geographic distribution of MPS IIIA, with an average global birth incidence of approximately 1 in 100,000.

MPS IIIA symptoms arise on average at 7 months of age, with the average age of diagnosis at 4.5 years for the majority of patients.[4] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[4] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[4,5,6] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction.[7] There are also reports of unexplained, recurrent and severe diarrhea.[7] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[7] A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[8]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase enzyme replacement therapy (ERT) for patients with MPS IIIA. A particular problem for lysosomal storage disorders that damage the brain such as MPS III is how to target ERT to the brain.[9] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[10,11]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the rhHNS clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase (rhHNS) has been developed specifically for delivery into the CSF via an IDDD due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine (FG), required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors. [12, 13, 14, 15]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[16] In this study, a patient with mucopolysaccharidosis Type I received 4 intrathecal doses of enzyme (Laronidase) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received intrathecal injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[17]

Several MPS I patients have been treated since 2005 with intrathecal Laronidase (recombinant α-L-Idurunonidase) in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of intrathecal ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358). This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse events monitoring, cerebrospinal fluid (CSF) laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of April 2010.[18]

Finally, the Sponsor of this current study has initiated a Phase I/II clinical trial titled, "A Safety and Dose Ranging Study of Idursulfase (Intrathecal) Administration Via an Intrathecal Drug Delivery Device in Pediatric Patients With Hunter Syndrome Who Have Central Nervous System Involvement and Are Receiving Treatment With Elaprase®" (clinicaltrials.gov identifier NCT00920647), which is using a comparable (IDDD drug route of administration and dosing regimen) to the current protocol. Given the similarity in dosing regimen any untoward safety signals from the idursulfase IT trial will be taken under careful consideration in this clinical trial.

1.2 Nonclinical Overview

Nonclinical studies indicate that IT administration of recombinant human heparan N sulfatase (rhHNS) leads to uptake by target CNS tissues. Preliminary PK and biodistribution results indicate that IT administration of rhHNS will provide the greatest chance of achieving a therapeutic effect in the Sanfilippo A population as compared to systemic administration. Likewise, CNS penetration from IV administration is unlikely to supply sufficient brain tissue levels to ameliorate the CNS manifestations of the disease. Thus, the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of MPS IIIA.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, the high dose of rhHNS was administered at 8.3 mg every other week (EOW). This translates into a 138 mg/kg brain weight dose (ie, based on a 60 g juvenile monkey brain). The CNS is considered a compartmentalized space, isolated by highly regulated flux mechanisms; thus, allometric scaling from animal to man is performed by normalizing doses to brain size.[19] No rhHNS-related adverse effects were noted at the highest dose; thus, an ~13.8 × safety margin relative to the starting clinical dose (10 mg, given EOW) in study HGT-SAN-055, and a ~3 × safety margin relative to the highest anticipated clinical dose (45 mg, given EOW) was achieved.

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of rhHNS into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg rhHNS resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis, astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21]

One-hundred ug rhHNS per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain); this is ~4.5 times the top human dose (45 mg) (human brain = ~1 kg). Efficacy at lower doses of rhHNS (eg, 20 ug, given IT, EOW or monthly) has been demonstrated.[10] A 20 ug injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (45 mg, EOW) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg rhHNS was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 Clinical Development Program

Study HGT-SAN-053 and Study HGT-SAN-055 comprise the current Shire HGT MPS IIIA clinical development program to registration. Study HGT-SAN-053 (also known as the Surrogate Endpoint Trial or SET) is an ongoing natural history study of untreated patients with MPS IIIA disease. The study endpoints in the SET study (neurocognitive and behavioral assessments; CSF, urine, and serum biomarkers; and brain MRI) have been chosen as direct comparators for the HGT-SAN-055 treatment study.

Study HGT-SAN-055 is a Phase I/II safety and ascending dose ranging study of recombinant human rhHNS administration via an intrathecal drug delivery device (IDDD) in patients with Sanfilippo Syndrome Type A (MPS IIIA). The Phase I/II study was designed to determine the safety, tolerability, and dose frequency via ascending IT dose regimens of rhHNS administered via an IDDD to patients age ≥3 years of age with MPS IIIA who have quantifiable evidence of CNS pathology early in the course of the disease. Patients who complete study HGT-SAN-055 and elect to continue to receive rhHNS IT treatment will comprise the patient population for HGT-SAN-067.

1.4 Extension Study Rationale

This extension study (Study HGT-SAN-067) will continue the evaluation of the effects of rhHNS administration on long-term safety and clinical activity and biomarker outcomes for patients who completed Study HGT-SAN-055 and elected to continue therapy with rhHNS.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 (patients who were dosed monthly) or Week 28 (patients who were dosed every other week) and completed the End of Study evaluations will be eligible for enrollment in this open-label extension study. All patients enrolled in the extension study will continue to receive rhHNS at the same dose and schedule as that received in Study HGT-SAN-055. The dose for each group will remain unchanged during this study unless safety and/or efficacy analyses of HGT-SAN-055 data indicate otherwise. Meaningful composite analysis of the optimum dose and regimen will come only after all 3 dose groups complete the entire HGT-SAN-055 study.

Study HGT-SAN-055 will be initiated in 2010. There is no clinical information available to date on the use of rhHNS. Please refer to the current edition of the rhHNS Investigator's Brochure for further information.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective(s) of this study is:

To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received rhHNS via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy.

2.2 Secondary Objectives

The secondary objectives of this study are:

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

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

To determine the long-term safety of intrathecal rhHNS administration, as measured by adverse events (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms, CSF chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

3.2 Secondary Endpoint

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in cerebrospinal fluid (CSF) and serum.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and CSF.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), aka Brainstem Auditory Evoked Potentials.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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 administration of 3 dose levels (10 mg and 45 mg once per month and 45 mg EOW) of rhHNS via an IDDD in patients with MPS IIIA who completed HGT-SAN-055 and elected to continue to receive rhHNS treatment. Patients will continue in the treatment group as previously received in the HGT SAN 055 study:

- Group 1: rhHNS administered by IT injection 10 mg once per month
- Group 2: rhHNS administered by IT injection 45 mg once per month
- Group 3: rhHNS administered by IT injection 45 mg EOW

It is anticipated that all patients successfully completing the HGT-SAN-055 study will elect to continue to receive IT rhHNS per their previous schedule in Study HGT-SAN-055 by consenting to participate, without interruption, in the HGT-SAN-067 extension study. Thus, for nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055.

Patients who participated in Study HGT-SAN-055 through Week 26 (patients dosed monthly) or Week 28 (patients dosed every other week) and completed the End of Study (EOS) will be eligible for enrollment after completing the HGT-SAN-055 EOS evaluations. Patients will be screened for entry into the study based on their completed participation in Study HGT-SAN-055. Once eligibility is confirmed, the Investigator will fully inform the patient's parent(s) or guardians(s) of the nature and scope of the study, potential risks and benefits of participation, the study procedures involved, and will answer all questions prior to the signing of the informed consent form. The informed consent must be obtained prior to performing any study-related procedures. Informed consent will be provided by the patient's parent/legal guardian(s) prior to the start of the extension study procedures.

Patients whose parents/legal guardians provide written informed consent/assent to participate in this study will check in with the study center 1 day prior to rhHNS dosing for safety assessments on each rhHNS treatment week. If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2 (±2 days). Patients will be discharged from the inpatient unit a minimum of 1 day following dosing with rhHNS and when deemed clinically stable by the Investigator.

The patient will have already received a standardized battery of neurodevelopmental assessments at the Baseline and 6-month time points in the HGT-SAN-055 study. These same assessments and tests will be performed at 12, 24, 36, and 48 months. Similarly, MRI of the head, ABR testing, CSF sampling by means of lumbar puncture and any other procedures requiring anesthesia will be performed at 12, 24, 36, and 48 months.

All patients will undergo end of study procedures 30 (±7) days following their last administration of rhHNS. End of study procedures will include a standard battery of 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 concomitant medications and AE monitoring.

All patients will be contacted by telephone for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS procedures to collect updated information on adverse events and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all administrations of rhHNS. However, if a patient's IDDD becomes nonfunctional or infected, it will be replaced so that the patient can remain on study. If use of the IDDD is precluded on a scheduled day of dosing, the IDDD will be declared a failure; no study drug will be administered, nor CSF sample obtained on that visit. Unlike the HGT-SAN-055 study, no study drug will be administered by lumbar puncture in this extension study. Upon declaration of failure, the IDDD will be removed and the patient scheduled for re-implantation of a new IDDD (see Section 7.11) at the earliest convenience, so that the patient may remain on, or remain as close as possible, to his/her original IT rhHNS dosing schedule. Note: Patients will require 1 week of recovery time from time of re-implantation, during which time the IDDD cannot be used, this may result in a delay in the next scheduled dose of rhHNS. The patient will resume his or her original dosing schedule; no catch-up dosing will occur.

If a patient discontinues the study, is withdrawn from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the End of Study Procedures.

An overview of the study appears in Appendix 1 Schedule of Events.

4.2 Rationale for Study Design and Control Group

Study HGT-SAN-055 is an ongoing Phase I/II safety and ascending dose ranging study of intrathecal administration of rhHNS via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of intrathecal rhHNS administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with rhHNS.

4.3 Study Duration and Dates

The study duration will have a maximum duration of 4 years of rhHNS treatment or until rhHNS is commercially available, the patient discontinues from the study, the Sponsor stops the study, or the Sponsor discontinues the development of rhHNS. Study completion will be defined as the time at which a patient completes 4 years of rhHNS treatment (including treatment in Study HGT-SAN-055), or transitions to commercially available rhHNS or discontinues from this study for other reasons.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue rhHNS treatment will be eligible to participate; a maximum of twelve patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. Patients must have completed all study requirements and assessments for Study HGT-SAN-055 prior to enrolling in this extension study and must have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board / Independent Ethics Committee-approved informed consent form after all relevant aspects of the study have been explained and discussed with the patient. The guardians' consent and patient's assent, as relevant, must be obtained.
3. The patient has received and tolerated treatment with rhHNS, completed the End of Study visit, and has received at least 80% of the total planned infusions within the last 6 months in study HGT-SAN-055 (ie, at least 5/6 ([Group 1 or 2] or 10/12 infusions [Group 3]).
4. Patients must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or at anytime during the study:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.
3. The patient has significant non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has significant MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a female patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.

7. The patient has a history of poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA or used any other intrathecal delivery device other than what was used in Study HGT-SAN-055, within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.
12. The patient's parent(s), or patient's legal guardian(s) is/are unable to provide consent or the patient cannot provide assent, as appropriate, due to, but not limited to, the inability to understand the nature, scope, and possible consequences of the study, or do/does not agree to comply with the protocol defined schedule of assessments.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

Recombinant human heparin N-sulfatase (rhHNS) drug product formulation is a sterile solution for injection in single-use vials for intrathecal (IT) administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, 0.005% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.

6.1.2 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment(s) Administered

rhHNS for IT administration will be provided by Shire HGT. rhHNS will be administered by an IDDD. Following the review and signing of informed consent, patients will receive the same dose of rhHNS they received in Study HGT-SAN-055:

- Group 1: rhHNS administered by IT injection 10 mg once per month
- Group 2: rhHNS administered by IT injection 45 mg once per month
- Group 3: rhHNS administered by IT injection 45 mg every other week (EOW)

6.3 Selection and Timing of Dose for Each Subject

The patient's dose of rhHNS will be the same dose (10 mg and 45 mg once per month and 45 mg EOW) they received in Study HGT-SAN-055. Patients will check in to the study center 1 day prior to intrathecal rhHNS dosing for safety assessments on each rhHNS treatment week, and if no safety concerns exist, will subsequently receive IT administration of rhHNS on Day 2. Patients will be discharged from the inpatient unit a minimum of 1 day following dosing with rhHNS and when deemed clinically stable by the Investigator.

The IT injections are to be administered 28 days (±7 days [groups 1 and 2]) and 14 days (±3 days [group 3]) apart. If a patient's IDDD becomes nonfunctional, it will be replaced so that the patient can remain on study. See Section 6.5 for a description on the replacement of a nonfunctional IDDD.

6.4 Cerebral Spinal Fluid Sample Procedure

A total of 10 mL of CSF will be obtained in two 5 mL aliquots prior to each injection for safety evaluation using the IDDD. A topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to CSF sampling. However, CSF will not be obtained if use of the IDDD is precluded, with the exception at the EOS visit, when it may be obtained by means of a lumbar puncture (LP). The performance of LP is at the discretion of the Investigator. An intracranial pressure (ICP) measurement will be obtained whenever a LP is performed.

If a lumbar puncture is to be performed, the patient will be anesthetized via general anesthesia with appropriate airway management. Once the patient is anesthetized, a lumbar puncture will be performed and a CSF sample will be obtained.

6.5 Intrathecal Administration of rhHNS

rhHNS will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive mild sedation to alleviate anxiety and/or to facilitate drug delivery.

Patients will then receive their appropriate dose of rhHNS via slow push/ injection over 2 to 5 minutes. Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during enzyme administration and through the next 24 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

If use of the IDDD is precluded on a scheduled day of dosing, the IDDD will be declared a failure; no study drug will be administered, nor CSF sample obtained on that visit. Unlike the HGT-SAN-055 study, no study drug will be administered by lumbar puncture in this extension study. Upon declaration of failure, the IDDD will be removed and the patient scheduled for re-implantation of a new IDDD (see Section 7.11) at the earliest convenience, so that the patient may remain on, or remain as close as possible, to his/her original IT rhHNS dosing schedule. Note: Patients will require 1 week of recovery time from time of re-implantation, during which time the IDDD cannot be used, this may result in a delay in the next scheduled dose of rhHNS. The patient will resume his or her original dosing schedule; no catch-up dosing will occur.

6.6 Method of Assigning Subjects to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with rhHNS. Patients will remain in the groups (1, 2, or 3) they were assigned to in Study HGT-SAN-055.

6.7 Blinding

Not applicable; this trial is not blinded.

6.8 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Reference List (WHODRL).

6.9 Restrictions

6.9.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than rhHNS or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.9.2 Fluid and Food Intake

Oral food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.9.3 Subject Activity Restrictions

There are no restrictions on patient activities in this study.

6.10 Treatment Compliance

rhHNS is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.11 Packaging and Labeling

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of rhHNS. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminum seal with a flip-off, plastic, tamper evident cap.

6.12 Storage and Accountability

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

6.13 Investigational Product Retention at Study Site

All rhHNS study drug delivered to an Investigator will be recorded and accounted for throughout the study. All rhHNS study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed after Sponsor approval per site policy after the study has been completed.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or legal guardian(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. The approximate maximum total blood, urine, and CSF volumes to be collected from each patient by the end of this study for safety assessments are presented in Table 7-1.

Table 7-1 Approximate Total Sample Volumes Collected Over the Duration of the Study From Each Patient by Group and Assay

	Groups 1 and 2	Group 3
Blood	290 mL	555 mL
Urine	530 mL	1,010 mL
CSF	480 mL	960 mL

Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory and/or Study Operations Manual.

7.2 Physical Examination

A physical examination of each patient will be performed as detailed in Appendix 1 Schedule of Events.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the baseline visit. If is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that same visit. See Section 7.9 for details. Note: Pressure-equalization tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) measurements will be taken once. All data will be recorded on the eCRF.

7.4 Head Circumference

Head circumference will be measured once. The data will be recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory and/or Study Operations Manual.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

7.7.2.1 Standard Serum Chemistry

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO2)
- Chloride (Cl)
- Creatinine
- Creatine kinase (CK) and subtypes
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

7.7.3 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.7.3.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory on urine samples:

- Macroscopic examination
- Microscopic examination of sediment
- pH

7.7.3.2 Urine Heparan Sulfate and Heparan Sulfate Derivatives

A urine sample will be collected for the determination of heparan sulfate and heparan sulfate derivatives and the analysis will be performed at Shire HGT laboratories. A urine sample from each visit will be reserved for possible, exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.4 Cerebrospinal Fluid Assessments

Cerebrospinal fluid (CSF) samples (10 ml in two 5 ml aliquots; labeled separately and processed according to the study operations manual) will be obtained from patients through an implanted IDDD. Should the IDDD become blocked or undergo mechanical complications, the CSF sample will not be obtained via lumbar puncture (LP), except when part of the EOS visit. The performance of LP is at the discretion of the Investigator. See Section 6.4 for further details.

CSF sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.4.1, 7.7.4.2, and 7.7.4.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites or protein or RNA may become available in the future (the samples maybe analyzed, if the assays are found applicable) and are thus not presently listed within this protocol.

7.7.4.1 CSF Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.4.2 CSF Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire HGT laboratories.

7.7.4.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of anti-rhHNS antibodies at Shire HGT laboratories.

7.7.4.4 CSF Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of MPS exploratory biomarkers at Shire HGT laboratories.

7.7.5 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual to be provided by Shire HGT.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded – see Section 6.4), prior to performing the MRI of the head, the ABR, the intracranial pressure (ICP), and the re-implantation of the IDDD (if applicable). See Appendix 1 for the Schedule of Events.

Note: the neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to co-operate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgement to initially estimate the extent of hearing loss (if any) during the initial physical examination. In this situation, specific evaluation of hearing loss will await examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will ask and offer the parent or guardian placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The auditory brainstem response (ABR) will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 MRI of the Head

The regional brain volume will be assessed through an MRI of the head. The patient will be under general anesthesia for this assessment. The central reading for MRI data, across all sites, will be completed at the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced so that the patient can remain on study. Procedures for implantation will be detailed in the device's Instructions for Use manual. The patient will be under general anesthesia for this procedure. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm device placement at the mid-thoracic level. A post-operative check of the IDDD will be performed on Day 7 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study. Drug can only be administered via the IDDD.

7.12 Intracranial Pressure Measurement

Intracranial pressure measurement (ICP) (centimeters of H2O) will be conducted per standard hospital practice. The measurement will be obtained whenever a LP is performed.

7.13 Dispensing Study Drug

rhHNS will be administered IT by means of an IDDD to patients in Dose Groups 1 and 2 on Day 2 (±2 days) of Week 1 of each treatment month and to patients in Dose Group 3 on Day 2 (±2 days) of Weeks 1 and 3 of each treatment month.

The patient may be mildly sedated for this procedure; rhHNS will be administered over 2 to 5 minutes. Please see Section 6.5 if the IDDD is not functioning.

The patient must not receive aspirin, non-steroidal anti-inflammatory medications, or medications that affect clotting within 1 week prior to each IT injection.

7.14 Pharmacokinetic Assessments

Pharmacokinetic assessments will not be included in this study.

7.15 Neurological Examination

A neurological examination to monitor CNS changes in patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

7.16 Serum Anti-rhHNS Antibody, Heparan Sulfate and Heparan Sulfate Derivative Determination

Blood samples will be collected prior to rhHNS injection and evaluated at Shire HGT laboratories for the determination of anti-rhHNS antibodies, heparan sulfate and heparan sulfate derivatives. Samples will be reserved for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two 5 mL blood samples will be collected from each patient at each designated time point. One 5 mL sample will be collected in a tube intended for serum specimens, while the second sample will be collected in a tube intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory and or Study Operations Manual.

7.17 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-2 and Table 7-3, respectively. See Appendix 3 for details on these assessments.

Table 7-2 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor	0 to 42 months: Bayley Scales of Infant Development-III (BSID-III) [23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II) [24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2) [25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III) [23]

Table 7-2 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition [26]

Table 7-3 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

Developmental or Cognitive Domain(s)	Sanfilippo Specific Assessments
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[4]

7.18 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's patients/legal guardian.

7.19 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.19.1, 7.19.2, and 7.19.3.

7.19.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study.

The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age

7.19.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being

7.19.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/guardian's life.

7.20 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHODRL.

7.21 Adverse Events

7.21.1 Adverse Events Assessments

Adverse events will be monitored continuously throughout the study from the time the patient, patient's parent/legal guardian signs the informed consent/assent (if applicable) until the safety follow-up contact or until the event has resolved or stabilized, or an outcome is reached, whichever comes first.

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

7.21.2 Definitions of Adverse Events and Serious Adverse Events

7.21.2.1 Adverse Event

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed, any adverse event prior to the start of study drug must be reported.

AEs include:

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

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

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

All adverse events should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for adverse events associated with intrathecal injections of rhHNS. In general, these adverse events can be classified as follows:

- Adverse events due to systemic exposure to rhHNS caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of rhHNS to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related adverse events.

Note: the classification of potential adverse events and the examples presented below are based on purely theoretical considerations and/or published literature as there is no human experience with intrathecal rhHNS therapy to date.

POTENTIAL ADVERSE EVENTS: INTRATHECAL RHHNS

Adverse Events Due To Systemic Exposure To rhHNS

Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

Adverse Events Related to the Direct Delivery of rhHNS to the CNS Through Intrathecal Administration

Examples of adverse events observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory parathesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time.

Potential Adverse Events: IDDD -Related Adverse Events

Examples of adverse events related to the insertion or use of an IDDD include, but are not limited to, the following: catheter disconnection or fracture, erosion of portal/catheter through the skin, fibrin sheath formation around catheter tip, hematoma, implant rejection, malposition of catheter, migration of portal/catheter, occlusion of portal/catheter, portal site or subcutaneous tract infection, and sepsis.

In addition, there are risks associated with intraspinal access, which include the following: cerebrospinal fluid leaks, dura mater or epidural vein perforation, epidural or intrathecal space infection (which could result in meningitis), inadvertent epidural placement, pain on injection, and spinal cord or nerve injury.

7.21.2.2 Serious Adverse Event

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

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity

- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 5) If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-4. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-4 Adverse Event Severity

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

Relationship of an adverse event or serious adverse event to study medication is to be determined by the Investigator based on the definitions in Table 7-5:

Table 7-5 Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	Unrelated to study drug.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the medication, follows a known or suspected response pattern to the medication, is confirmed by improvement upon stopping the medication (dechallenge) and reappears upon repeated exposure (rechallenge).

Table 7-5 Adverse Event Relatedness

Relationship to Product(s)	Definition
	Note that this is not to be construed as requiring re-exposure of the patient to study drug; however, the determination of definitely related can only be used when recurrence of event is observed.

7.21.3 Procedures for Recording and Reporting Adverse Events

7.21.3.1 Reporting Serious Adverse Events

Any SAE, regardless of relationship to study medication, which occurs in a patient after informed consent, should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study drug or device. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

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

Shire Pharmacovigilance and Risk Management Department:

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

AND

Shire HGT Medical Monitor: [redacted], MD

[redacted]

FAX: [redacted] (USA)

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

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

If an SAE is assessed as severe and unexpected, or life-threatening, contact:

[redacted] MD
[redacted]
Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139, USA
Telephone: [redacted]
Fax: [redacted] (USA)
Mobile: [redacted]
[redacted]

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/ MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

7.21.3.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. In addition, the relationship of each AE to study medication must be recorded.

7.21.3.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results. The Investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire HGT Medical Monitor (see Section 7.21.3.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient. The Investigator or other physician in attendance in such an emergency must contact the Shire HGT Medical Monitor as soon as possible.

The Investigator, along with the Shire HGT Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.22 Pregnancy

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

7.23 Removal of Subjects from the Trial or Study Drug

The patient's parent or legal guardian acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If for any reason the patient refuses treatment during the study, the patient will be withdrawn from the study, and the reason for refusal will be documented on the eCRF. Reasonable efforts will be made to monitor the patient for AEs following such discontinuation. Such efforts will be documented in the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized guardian may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.

- Clinically problematic intubations or extubations which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.

If a patient or the patient's legal guardian(s), acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, the Patient Completion/Discontinuation Case Report Form (eCRF) describing the reason for discontinuation must be completed. Any adverse events (AE's) experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.24 Other Study Procedures

This section is not applicable.

7.25 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers will provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 (patients who were dosed monthly) or Week 28 (patients who were dosed every other week) and completed the End of Study evaluations will be eligible for enrollment in this open-label extension study. Informed consent will be provided by the patient's parent(s)/legal guardian(s) prior to start of extension study procedures.

If there are no safety concerns, patients who were previously treated with intrathecal rhHNS in Study HGT-SAN-055 and elect to continue rhHNS treatment will continue receiving monthly (Groups 1 and 2) or EOW (Group 3) intrathecal rhHNS in this extension study, as described in Appendix 1 Schedule of Events.

8.1 Screening Visit/Baseline Visit

All Screening assessments for this study are to have been performed during the Week 26 (Groups 1 and 2) or Week 28 (Group 3) (30 [±7] days after the last rhHNS administration) EOS procedures in HGT-SAN-055. If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, the assessments detailed in this Screening visit are not required to be repeated. The Baseline Visit for this study will be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal rhHNS dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Serum chemistry
- Urinalysis
- Neurological examination (performed prior to the administration of anesthesia)
- Neurodevelopmental assessments (performed prior to the administration of anesthesia
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
  - ABR
  - MRI of the head
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Urine heparan sulfate and heparan sulfate derivatives

- Serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Monthly, Weekly Assessments

Patients in Dose Groups 1 and 2 will receive rhHNS IDDD monthly, on Week 1, Day 2 (±2 days). Patients in dose Group 3 will receive rhHNS EOW, on Weeks 1 and 3, Day 2 (±2 days).

8.2.1 Week 1 (Groups 1 and 2); Week 1 and 3 (Group 3)

8.2.1.1 Day 1 (Pre-treatment) Assessments

- Informed consent (Week 1, Month 1 only) prior to study HGT-SAN-067 study procedures
- Physical examination
- Height and weight
- Vital signs
- Hematology
- Serum Chemistry
- Urinalysis
- Neurological Examination (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Concomitant Medications, Therapies, and Procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or Screening) assessments were performed within 7 days of first intrathecal rhHNS treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED ONLY AT MONTHS 12, 24, 36, AND 48

- Head circumference
- Visual and hearing assessments
- Urine Heparan Sulfate and Heparan Sulfate Derivatives (Group 3: obtained only at first week of each treatment month)
- Serum Heparan Sulfate and Heparan Sulfate Derivatives (Group 3: obtained only at first week of each treatment month)

- Anti-rhHNS antibody testing
- Auditory Brainstem Response (ABR)
- MRI of the head
- Full neurodevelopmental testing (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and IDDD Injection of rhHNS

- Physical examination
- ECG (performed following IT study drug injection)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- rhHNS IT injection (Day 2 ±2 days)
- neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

8.2.1.3 Day 3 (Post IT Dose) Assessments

Patients will be discharged when deemed clinically stable by the Investigator.

- Vital signs
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

8.3 End of Study/ Early Termination Procedures

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of rhHNS. Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the end of study procedures at time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: scheduled removal of the IDDD will be required at study completion with sedation or anesthesia, as required.

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing

- ECG
- Vital signs
- Hematology
- Serum Chemistries
- Urinalysis
- Urine Heparan Sulfate and Heparan Sulfate Derivatives
- Serum Heparan Sulfate and Heparan Sulfate Derivatives
- Anti-rhHNS antibody testing
- Auditory Brainstem Response (ABR)
- MRI of the head
- CSF sample collection
- Neurological examination
- Full neurodevelopmental testing
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

8.4 Safety Follow-up Visit (by Telephone)

Patients who complete the study will have a safety follow-up visit 30 Days (±7 days)

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the safety follow-up visit at the time of discontinuation. Participation in these procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study.

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire HGT or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of rhHNS in patients with Sanfilippo syndrome type A (MPS IIIA). The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg per month, 45 mg per month and 45 mg every other week) with respect to demographic and baseline characteristics, efficacy variables and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time.

All hypothesis tests will be 2-sided and will be performed at the 0.05 level. Hypothesis testing will be viewed as exploratory. Any resulting p-values will not be regarded as a firm support for conclusions, but rather suggestive of areas of examination in future studies. In general, variables will be quantified as a change from the baseline value. The null hypothesis will be that there is no difference in the change from baseline between dose groups. Note that the baseline visit for this study will be the first day the patient received his/her IT dose of rhHNS in study HGT-SAN-055.

The primary objective of this trial is to assess the long term safety of rhHNS administration via a surgically implanted intrathecal drug delivery device (IDDD). Hence an extensive safety assessment will be performed. The safety analyses will consist of all enrolled patients. To evaluate safety, adverse experiences will be tabulated by dose group. Vital signs, electrocardiograms, serum and CSF components and chemistries, hematology, and urinalysis safety monitoring will be listed for each patient and abnormal values will be flagged. In addition, anti-rhHNS antibodies (in CSF and serum) will also be listed. No formal statistical tests will be performed on the safety parameters.

10.2 Determination of Sample Size

Since this is an extension study, sample size is determined by the number of patients who completed HGT-SAN-055 (maximum of 12 patients) and enrolled in this study

10.3 Analysis Populations

The analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. Both safety and efficacy analyses would be performed using the above mentioned population.

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew, by dose group. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of treatment-emergent adverse events, due to study drug and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients will be included in the safety analysis. Patients will be grouped according to the actual dose received.

No formal statistical test will be performed in the safety evaluations. Vital sign measurements, clinical chemistry, and hematology safety monitoring will be listed for each patient, and abnormal values will be flagged. These will also be summarized at each time point, including change from baseline.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 9.0 or later. In all cases (with the exception of device-related events), adverse event summaries will be based on all adverse event recorded beginning on Study Day 1 (treatment-emergent AEs).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in system organ class, and having each individual adverse event. Note that in any given category (eg, system organ class) a patient will only be counted once. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication.

Adverse events that occur up to 30 days after the last dose of study drug will be considered "on-treatment". Adverse events which are deemed probably or possibly related to the device will be summarized by dose group and overall.

Laboratory data will be listed by patient and dose group. Patients with newly occurring abnormalities outside the normal range will be flagged and listed separately and summarized. Mean change from baseline values or shift tables will also be provided by dose group at each visit.

Vital signs data will be listed by patient and dose group. Furthermore, mean changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

ECG assessments will be listed by patient and dose group. Mean changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.1.2 Clinical Laboratory Evaluations

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis) results will be presented in summary tables by evaluation visit using number of patients (n), mean, median, standard deviation, minimum, and maximum. Changes from baseline will be summarized for each post-baseline visit. The number of patients with clinically significant laboratory results or abnormal results during the study period will be presented in shift tables.

For the laboratory measurements, shift tables will be presented in terms of Low (L), Normal (N), High (H), Missing (M). High and Low measurements will be based on reference ranges provided by the laboratory at the study site.

Clinical laboratory results will also be presented in data listings.

10.6.1.3 Anti-rhHNS Antibody Formation

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by assay methodology used to identify antibodies, number and percentage of positive and negative specimens by evaluation visit and/or study week, and number and percentage of positive and negative specimens overall. These results will also be presented in data listings.

10.6.2 Secondary Analysis

10.6.2.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of rhHNS administration on QoL measures will be examined by presenting mean change from baseline across dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.2.2 Pharmacodynamic Analyses

To determine the effects of rhHNS administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparin sulfate reduction (in CSF and urine) will be examined using mean change and the corresponding 95% confidence interval. The concentration of inflammatory cytokines in serum and CSF will also be examined. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

The planned analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki (2008).

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol. Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. On-site review of the eCRF's for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the electronic clinical report form (eCRF). The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

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

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire HGT. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire HGT.

11.8 Data Monitoring Committee

There will be no data monitoring committee for this study.

11.9 Protocol Violations/Deviations

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

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 9.0 or later. Concomitant medication will be coded using WHODRL. Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire HGT and the Investigators. In addition, a decision on the part of Shire HGT to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

12 REFERENCE LIST

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Appendix 1 Schedule of Events

Table 1 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Groups 1 and 2)

		Week 1 Each Treatment Month					
Assessment	**Screening/ Baseline Visit[i]**	**Pre-Tx Day 1[a, l]**	**IT administration Day 2**	**Day 3[d]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Informed Consent/Enrollment		●					
Physical Examination	●	●	●			●	
Height and Weight	●	●				●	
Head Circumference	●				●	●	
Visual and Hearing Assessment					●	●	
ECG	●		●[b]			●	
Vital Signs	●	●	●	●		●	
Hematology	●	●				●	
Serum Chemistry	●	●				●	
Urinalysis	●	●				●	
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Serum Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[j]	●				●	●	
Auditory Brainstem Response (ABR)	●				●	●	
MRI of the Head	●				●	●	
CSF Sample Collection[k]	●		●[c]			●[c]	
rhHNS administration[g]			●				
Neurological Examination	●	●	●	●		●	
Full Neurodevelopmental Testing	●				●	●	
Children's Sleep Habits Rating Scale	●				●	●	
Child Health Questionnaire-50	●				●	●	
Child Health Questionnaire-87	●				●	●	
Infant Toddler QOL Questionnaire	●				●	●	

Table 1 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Groups 1 and 2)

		Week 1 Each Treatment Month					
Assessment	**Screening/ Baseline Visit[i]**	**Pre-Tx Day 1[a, l]**	**IT administration Day 2**	**Day 3[d]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Concomitant Medications, Therapies, and Procedures	●	●	●	●		●	●
Adverse Event Monitoring	●	●	●	●		●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; ECG = electrocardiogram; MRI = Magnetic resonance imaging; TX = treatment;

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] A total of 10 mLs of CSF will be obtained in two 5 mL aliquots (labeled separately – process according to study operations manual). An attempt will be made to obtain CSF sample via the IDDD prior to each administration of rhHNS and at the End of Study visit. If it is not possible to obtain CSF using the IDDD, the IDDD will be replaced. See Section 6.4 for details.

[d] Patients will be discharged when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced so that the patient can remain on study. See Section 6.5.

[h] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[i] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled rhHNS IT dose.

[j] Blood sample drawn before IT injection of rhHNS.

[k] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

Table 2 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Group 3)

		Week 1 and 3 Each Treatment Month					
Assessment	**Screening/Baseline Visit[i]**	**Pre-Tx Day 1[a]**	**IT administration Day 2**	**Day 3[d,]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Informed Consent/Enrollment		●					
Physical Examination	●	●	●			●	
Height and Weight	●	●				●	
Head Circumference	●				●	●	
Visual and Hearing Assessment					●	●	
ECG	●		●[b]			●	
Vital Signs	●	●	●	●		●	
Hematology	●	●				●	
Serum Chemistry	●	●				●	
Urinalysis	●	●				●	
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Serum Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[j]	●				●	●	
Auditory Brainstem Response (ABR)	●				●	●	
MRI of the Head	●				●	●	
CSF Sample Collection[k]	●		●[c]			●[c]	
rhHNS administration[g]			●				
Neurological Examination	●	●	●	●[j]		●	
Full Neurodevelopmental Testing	●				●	●	
Children's Sleep Habits Rating Scale	●				●	●	
Child Health Questionnaire-50	●				●	●	
Child Health Questionnaire-87	●				●	●	
Infant Toddler QOL Questionnaire	●				●	●	

Table 2 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Group 3)

		Week 1 and 3 Each Treatment Month					
Assessment	**Screening/Baseline Visit[i]**	**Pre-Tx Day 1[a]**	**IT administration Day 2**	**Day 3[d,]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Concomitant Medications, Therapies, and Procedures	●	●	●	●		●	●
Adverse Event Monitoring	●	●	●	●		●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; ECG = electrocardiogram; MRI = Magnetic resonance imaging ; TX = treatment;

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] A total of 10 mLs of CSF will be obtained in two 5 mL aliquots (labeled separately – process according to study operations manual). An attempt will be made to obtain CSF sample via the IDDD prior to each administration of rhHNS and at the End of Study visit. If it is not possible to obtain CSF using the IDDD, the IDDD will be replaced. See Section 6.4 for details.

[d] Patients will be discharged when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced so that the patient can remain on study. See Section 6.5.

[h] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[i] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled rhHNS IT dose.

[j] Blood sample drawn before IT injection of rhHNS.

[k] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

Appendix 2 Sample Neurological Exam

☐ Not Done, Please provide reason: _____

Exam date: _____ (Day/Mon/Year) Name of Examiner: _____

Overall neurological impression	☐ Normal ☐ Abnormal

Please mark normal, abnormal, or unable to determine for each item listed. If any abnormalities are found, please specify the findings in the space provided.

Items	Status	Please describe abnormalities
Observation and mental status		
Alertness	☐ Normal ☐ Abnormal ☐ Not Done	
Interaction with care taker	☐ Normal ☐ Abnormal ☐ Not Done	
Activity level	☐ Normal ☐ Abnormal ☐ Not Done	
Involuntary movements	☐ Absent ☐ Present ☐ Not Done	
Cranial nerves		
Pupillary reaction to light	☐ Normal ☐ Abnormal ☐ Not Done	
Extra ocular movements	☐ Normal ☐ Abnormal ☐ Not Done	
Eye closure	☐ Normal ☐ Abnormal	

Items	Status	Please describe abnormalities
	☐ Not Done	
Facial symmetry	☐ Normal ☐ Abnormal ☐ Not Done	
Coordination/Sensory		
Rapid finger tapping	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Finger to nose	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Stand on one foot	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Hop on one foot	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Romberg	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Deep tendon reflexes		
Biceps	☐ Normal ☐ Abnormal ☐ Not Done	
Patellar	☐ Normal ☐ Abnormal ☐ Not Done	
Ankle	☐ Normal	

Items	Status	Please describe abnormalities
	☐ Abnormal ☐ Not Done	
Deep tendon reflexes (continue)		
Ankle clonus	☐ Absent ☐ Present ☐ Not done	
Gait		
Natural walking	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Straight line walking	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Tandem walking	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Other		
Specify: _____	☐ Normal ☐ Abnormal	
Specify: _____	☐ Normal ☐ Abnormal	
Specify: _____	☐ Normal ☐ Abnormal	

Items	Status	Please describe abnormalities
Specify: _____	☐ Normal ☐ Abnormal	

Appendix 3 Neurodevelopmental and Behavioral Assessments

Table 3-1 and Table 3-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table 3-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table 3-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[4]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child's abilities to perform certain skills (sitting, walking, and talking). However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III)[23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]

Purpose:

The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 4 Investigator's Signature

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

Final Date: 21 June 2010

Amendment 1 Date: N/A

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

Signed: _____ Date: _____

[redacted], MD
[redacted]

[redacted], UK
[redacted]

Signed: _____ Date: _____

[redacted] MD
[redacted]
Medical Monitor

Shire HGT
700 Main Street
Cambridge, MA 01239

[redacted]

Appendix 5 The National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever). ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES. ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis.						
ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter

Sponsor: Shire

Medical Monitor: [redacted], MD
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Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139, USA
Telephone: [redacted]
Fax: [redacted] (USA)

	Date
Original Protocol:	21 June 2010
Amendment 1	27 January 2011

SYNOPSIS

Sponsor:

Shire

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS)

Name of Active Ingredient:

rhHNS

Name of Inactive Ingredient:

N/A

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

Study Phase: I/II

Primary Objective:

To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received rhHNS via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy.

Secondary Objectives:

To collect as indications 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.

Study Endpoints:

The primary endpoint of this study is:

To determine the long-term safety of intrathecal rhHNS administration, as measured by adverse events (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms, cerebrospinal fluid (CSF) chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in cerebrospinal fluid (CSF) and serum.
- Concentration of inflammatory cytokines in serum and CSF.

- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and CSF
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), aka Brainstem Auditory Evoked Potentials.

Study Design:

This is a multicenter, multiple-dose, open-label extension of Study HGT-SAN-055 designed to evaluate the long-term safety and clinical activity and biomarker outcomes of intrathecal administration of 3 dose levels (10 mg and 45 mg once per month and 45 mg every other week [EOW]) of rhHNS via an IDDD in patients with MPS IIIA.

Patients will continue in the treatment group as they participated in the HGT-SAN-055 study:

- Group 1: rhHNS administered by IT injection 10 mg once per month for a total of 6 months
- Group 2: rhHNS administered by IT injection 45 mg once per month for a total of 6 months
- Group 3: rhHNS administered by IT injection 45 mg EOW for a total of 6 months

It is anticipated that all patients successfully completing the HGT-SAN-055 study will elect to continue to receive intrathecal (IT) rhHNS per their previous schedule in Study HGT-SAN-055 by consenting to participate, without interruption, in the HGT-SAN-067 extension study. Thus, for nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055.

Patients whose parents/legal guardians provide written informed consent/assent to participate in this study will check in with the study center 1 day prior to rhHNS dosing for safety assessments on each rhHNS treatment week. If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2. Patients will be discharged from the inpatient unit a minimum of 1 day following dosing with rhHNS and when deemed clinically stable by the Investigator. The patient will have already received a standardized battery of neurodevelopmental assessments at the baseline and 6 month time points in the HGT-SAN-055 study. These same assessments and tests will also be performed at 12, 24, 36, and 48 months. Similarly, MRI of the head, ABR testing, CSF sampling via lumbar puncture and any other procedures requiring anesthesia will be performed at 12, 24, 36, and 48 months.

All patients will undergo end of study procedures 30 (±7) days following their last administration of rhHNS. End of study (EOS) procedures will include a standard battery of clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, ABR, and MRI.

All patients will be contacted by telephone for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS procedures to collect updated information on adverse events and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all administrations of rhHNS. However, if a patient's IDDD becomes nonfunctional or infected, it will be replaced so that the patient can remain on the study.

If use of the IDDD is precluded on a scheduled day of dosing, the IDDD will be declared a failure; no study drug will be administered, nor CSF sample obtained on that visit. Unlike the HGT-SAN-055 study, no study drug will be administered by lumbar puncture in this extension study. Upon declaration of failure, the IDDD will be removed and the patient scheduled for re-implantation of a new IDDD at the earliest convenience, so that the patient may remain on, or remain as close as possible, to his/her original IT rhHNS dosing schedule. Note: Patients will require 1 week of recovery time from time of re-implantation, during which time the IDDD cannot be used, this may result in a delay in the next scheduled dose of rhHNS. The patient will resume his or her original dosing schedule; no catch-up dosing will occur.

If a patient discontinues or is withdrawn from the study or the study is stopped by the Sponsor, the IDDD will be removed as part of the End of Study Procedures.

Study Population:

A maximum of twelve patients are planned for this study. To be eligible for participation, patients will have completed all study requirements in Study HGT-SAN-055 and will have elected to continue treatment with rhHNS.

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

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

1. Patients must have completed all study requirements and assessments for Study HGT-SAN-055 prior to enrolling in this extension study and must have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board / Independent Ethics Committee-approved informed consent form after all relevant aspects of the study have been explained and discussed with the patient. The guardians' consent and patient's assent, as relevant, must be obtained.
3. The patient has received and tolerated treatment with rhHNS, completed the End of Study visit, and has received at least 80% of the total planned infusions within the last 6 months in study HGT-SAN-055, (ie, at least 5/6 ([Group 1 or 2] or 10/12 infusions [Group 3]).
4. Patients must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or at anytime during the study:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.

3. The patient has significant non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has significant MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a female patient of childbearing potential, who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA or used any other intrathecal delivery device other than what was used in Study HGT-SAN-055, within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.
12. The patient's parent(s), or patient's legal guardian(s) is/are unable to provide consent or the patient cannot provide assent, as appropriate, due to, but not limited to, the inability to understand the nature, scope, and possible consequences of the study, or do/does not agree to comply with the protocol defined schedule of assessments.

Test Product; Dose; and Mode of Administration:
Recombinant human heparan N-sulfatase (rhHNS) will be administered via an IDDD according to the same dosing regimen to which the patient was assigned in HGT-SAN-055 (ie, 10 mg monthly, 45 mg monthly, or 45 mg EOW).

Reference Therapy; Dose; and Mode of Administration: Not Applicable

Duration of Treatment:

The study duration will be 4 years.

Pharmacokinetic Variables:

Pharmacokinetics will not be assessed in this study.

Safety Assessments:
Safety evaluations will include vital signs, physical examinations, adverse event (AE) assessments, and electrocardiograms (ECG); serum chemistry, hematology, and urine laboratory tests; and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods:
The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial.

Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time which may be attributed to treatment. For continuous data, 95% confidence interval around the mean will be presented.

The analysis population consists of all eligible patients from HGT-SAN-055, who have agreed to participate in the extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 1: 27 January 2011

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABR	Auditory Brainstem Response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CNS	central nervous system
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CO_2	carbon dioxide
CRO	contract research organization
CSF	cerebrospinal fluid
DDD	drug delivery device
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
FDA	Food and Drug Administration
FG	formylglycine

FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonisation
ICP	intracranial pressure
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgE	immunoglobulin E
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MABC-2	Movement Assessment Battery for Children, Second Edition

MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
QoL	quality of life
PE	pressure-equalization
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)
WHODRL	World Health Organization Drug Reference List

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. The patient's treatment group, dosing regimen, and the intrathecal drug delivery device (IDDD) will be the same as that employed in study HGT-SAN-055.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is a lysosomal storage disease (LSD) caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. MPS IIIA results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtypes A and B similar in prevalence, accounting for approximately 90% of all cases of MPS III.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1, 2, 3] In summary, there is widespread geographic distribution of MPS IIIA, with an average global birth incidence of approximately 1 in 100,000.

MPS IIIA symptoms arise on average at 7 months of age, with the average age of diagnosis at 4.5 years for the majority of patients.[4] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[4] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[4,5,6] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction.[7] There are also reports of unexplained, recurrent and severe diarrhea.[7] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[7] A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[8]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase enzyme replacement therapy (ERT) for patients with MPS IIIA. A particular problem for lysosomal storage disorders that damage the brain such as MPS III is how to target ERT to the brain.[9] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[10, 11]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the rhHNS clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase (rhHNS) has been developed specifically for delivery into the CSF via an IDDD due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine (FG), required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors. [12, 13, 14, 15]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[16] In this study, a patient with mucopolysaccharidosis Type I received 4 intrathecal doses of enzyme (Laronidase) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received intrathecal injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[17]

Several MPS I patients have been treated since 2005 with intrathecal Laronidase (recombinant α-L-Idurunonidase) in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of intrathecal ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358). This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse events monitoring, cerebrospinal fluid (CSF) laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of April 2010.[18]

Finally, the Sponsor of this current study has initiated a Phase I/II clinical trial titled, "A Safety and Dose Ranging Study of Idursulfase (Intrathecal) Administration Via an Intrathecal Drug Delivery Device in Pediatric Patients With Hunter Syndrome Who Have Central Nervous System Involvement and Are Receiving Treatment With Elaprase®" (clinicaltrials.gov identifier NCT00920647), which is using a comparable (IDDD drug route of administration and dosing regimen) to the current protocol. Given the similarity in dosing regimen any untoward safety signals from the idursulfase IT trial will be taken under careful consideration in this clinical trial.

1.2 Nonclinical Overview

Nonclinical studies indicate that IT administration of recombinant human heparan N sulfatase (rhHNS) leads to uptake by target CNS tissues. Preliminary PK and biodistribution results indicate that IT administration of rhHNS will provide the greatest chance of achieving a therapeutic effect in the Sanfilippo A population as compared to systemic administration. Likewise, CNS penetration from IV administration is unlikely to supply sufficient brain tissue levels to ameliorate the CNS manifestations of the disease. Thus, the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of MPS IIIA.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, the high dose of rhHNS was administered at 8.3 mg every other week (EOW). This translates into a 138 mg/kg brain weight dose (ie, based on a 60 g juvenile monkey brain). The CNS is considered a compartmentalized space, isolated by highly regulated flux mechanisms; thus, allometric scaling from animal to man is performed by normalizing doses to brain size.[19] No rhHNS-related adverse effects were noted at the highest dose; thus, an ~13.8 × safety margin relative to the starting clinical dose (10 mg, given EOW) in study HGT-SAN-055, and a ~3 × safety margin relative to the highest anticipated clinical dose (45 mg, given EOW) was achieved.

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of rhHNS into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg rhHNS resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis, astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21]

One-hundred ug rhHNS per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain); this is ~4.5 times the top human dose (45 mg) (human brain = ~1 kg). Efficacy at lower doses of rhHNS (eg, 20 ug, given IT, EOW or monthly) has been demonstrated.[10] A 20 ug injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (45 mg, EOW) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg rhHNS was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 Clinical Development Program

Study HGT-SAN-053 and Study HGT-SAN-055 comprise the current Shire HGT MPS IIIA clinical development program to registration. Study HGT-SAN-053 (also known as the Surrogate Endpoint Trial or SET) is an ongoing natural history study of untreated patients with MPS IIIA disease. The study endpoints in the SET study (neurocognitive and behavioral assessments; CSF, urine, and serum biomarkers; and brain MRI) have been chosen as direct comparators for the HGT-SAN-055 treatment study.

Study HGT-SAN-055 is a Phase I/II safety and ascending dose ranging study of recombinant human rhHNS administration via an intrathecal drug delivery device (IDDD) in patients with Sanfilippo Syndrome Type A (MPS IIIA). The Phase I/II study was designed to determine the safety, tolerability, and dose frequency via ascending IT dose regimens of rhHNS administered via an IDDD to patients age ≥3 years of age with MPS IIIA who have quantifiable evidence of CNS pathology early in the course of the disease. Patients who complete study HGT-SAN-055 and elect to continue to receive rhHNS IT treatment will comprise the patient population for HGT-SAN-067.

1.4 Extension Study Rationale

This extension study (Study HGT-SAN-067) will continue the evaluation of the effects of rhHNS administration on long-term safety and clinical activity and biomarker outcomes for patients who completed Study HGT-SAN-055 and elected to continue therapy with rhHNS.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 (patients who were dosed monthly) or Week 28 (patients who were dosed every other week) and completed the End of Study evaluations will be eligible for enrollment in this open-label extension study. All patients enrolled in the extension study will continue to receive rhHNS at the same dose and schedule as that received in Study HGT-SAN-055. The dose for each group will remain unchanged during this study unless safety and/or efficacy analyses of HGT-SAN-055 data indicate otherwise. Meaningful composite analysis of the optimum dose and regimen will come only after all 3 dose groups complete the entire HGT-SAN-055 study.

Study HGT-SAN-055 will be initiated in 2010. There is no clinical information available to date on the use of rhHNS. Please refer to the current edition of the rhHNS Investigator's Brochure for further information.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective(s) of this study is:

To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received rhHNS via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy.

2.2 Secondary Objectives

The secondary objectives of this study are:

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

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

To determine the long-term safety of intrathecal rhHNS administration, as measured by adverse events (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms, CSF chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

3.2 Secondary Endpoint

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in cerebrospinal fluid (CSF) and serum.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and CSF.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), aka Brainstem Auditory Evoked Potentials.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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 administration of 3 dose levels (10 mg and 45 mg once per month and 45 mg EOW) of rhHNS via an IDDD in patients with MPS IIIA who completed HGT-SAN-055 and elected to continue to receive rhHNS treatment. Patients will continue in the treatment group as previously received in the HGT SAN 055 study:

- Group 1: rhHNS administered by IT injection 10 mg once per month
- Group 2: rhHNS administered by IT injection 45 mg once per month
- Group 3: rhHNS administered by IT injection 45 mg EOW

It is anticipated that all patients successfully completing the HGT-SAN-055 study will elect to continue to receive IT rhHNS per their previous schedule in Study HGT-SAN-055 by consenting to participate, without interruption, in the HGT-SAN-067 extension study. Thus, for nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055.

Patients who participated in Study HGT-SAN-055 through Week 26 (patients dosed monthly) or Week 28 (patients dosed every other week) and completed the End of Study (EOS) will be eligible for enrollment after completing the HGT-SAN-055 EOS evaluations. Patients will be screened for entry into the study based on their completed participation in Study HGT-SAN-055. Once eligibility is confirmed, the Investigator will fully inform the patient's parent(s) or guardians(s) of the nature and scope of the study, potential risks and benefits of participation, the study procedures involved, and will answer all questions prior to the signing of the informed consent form. The informed consent must be obtained prior to performing any study-related procedures. Informed consent will be provided by the patient's parent/legal guardian(s) prior to the start of the extension study procedures.

Patients whose parents/legal guardians provide written informed consent/assent to participate in this study will check in with the study center 1 day prior to rhHNS dosing for safety assessments on each rhHNS treatment week. If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2 (±2 days). Patients will be discharged from the inpatient unit a minimum of 1 day following dosing with rhHNS and when deemed clinically stable by the Investigator.

The patient will have already received a standardized battery of neurodevelopmental assessments at the Baseline and 6-month time points in the HGT-SAN-055 study. These same assessments and tests will be performed at 12, 24, 36, and 48 months. Similarly, MRI of the head, ABR testing, CSF sampling by means of lumbar puncture and any other procedures requiring anesthesia will be performed at 12, 24, 36, and 48 months.

All patients will undergo end of study procedures 30 (±7) days following their last administration of rhHNS. End of study procedures will include a standard battery of 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 concomitant medications and AE monitoring.

All patients will be contacted by telephone for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS procedures to collect updated information on adverse events and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver all administrations of rhHNS. However, if a patient's IDDD becomes nonfunctional or infected, it will be replaced so that the patient can remain on study. If use of the IDDD is precluded on a scheduled day of dosing, the IDDD will be declared a failure; no study drug will be administered, nor CSF sample obtained on that visit. Unlike the HGT-SAN-055 study, no study drug will be administered by lumbar puncture in this extension study. Upon declaration of failure, the IDDD will be removed and the patient scheduled for re-implantation of a new IDDD (see Section 7.11) at the earliest convenience, so that the patient may remain on, or remain as close as possible, to his/her original IT rhHNS dosing schedule. Note: Patients will require 1 week of recovery time from time of re-implantation, during which time the IDDD cannot be used, this may result in a delay in the next scheduled dose of rhHNS. The patient will resume his or her original dosing schedule; no catch-up dosing will occur.

If a patient discontinues the study, is withdrawn from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the End of Study Procedures.

An overview of the study appears in Appendix 1 Schedule of Events.

4.2 Rationale for Study Design and Control Group

Study HGT-SAN-055 is an ongoing Phase I/II safety and ascending dose ranging study of intrathecal administration of rhHNS via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of intrathecal rhHNS administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with rhHNS.

4.3 Study Duration and Dates

The study duration will be 4 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue rhHNS treatment will be eligible to participate; a maximum of twelve patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. Patients must have completed all study requirements and assessments for Study HGT-SAN-055 prior to enrolling in this extension study and must have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board / Independent Ethics Committee-approved informed consent form after all relevant aspects of the study have been explained and discussed with the patient. The guardians' consent and patient's assent, as relevant, must be obtained.
3. The patient has received and tolerated treatment with rhHNS, completed the End of Study visit, and has received at least 80% of the total planned infusions within the last 6 months in study HGT-SAN-055 (ie, at least 5/6 ([Group 1 or 2] or 10/12 infusions [Group 3]).
4. Patients must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or at anytime during the study:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.
3. The patient has significant non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has significant MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a female patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.

7. The patient has a history of poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA or used any other intrathecal delivery device other than what was used in Study HGT-SAN-055, within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.
12. The patient's parent(s), or patient's legal guardian(s) is/are unable to provide consent or the patient cannot provide assent, as appropriate, due to, but not limited to, the inability to understand the nature, scope, and possible consequences of the study, or do/does not agree to comply with the protocol defined schedule of assessments.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

Recombinant human heparin N-sulfatase (rhHNS) drug product formulation is a sterile solution for injection in single-use vials for intrathecal (IT) administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, 0.005% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.

6.1.2 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment(s) Administered

rhHNS for IT administration will be provided by Shire HGT. rhHNS will be administered by an IDDD. Following the review and signing of informed consent, patients will receive the same dose of rhHNS they received in Study HGT-SAN-055:

- Group 1: rhHNS administered by IT injection 10 mg once per month
- Group 2: rhHNS administered by IT injection 45 mg once per month
- Group 3: rhHNS administered by IT injection 45 mg every other week (EOW)

6.3 Selection and Timing of Dose for Each Subject

The patient's dose of rhHNS will be the same dose (10 mg and 45 mg once per month and 45 mg EOW) they received in Study HGT-SAN-055. Patients will check in to the study center 1 day prior to intrathecal rhHNS dosing for safety assessments on each rhHNS treatment week, and if no safety concerns exist, will subsequently receive IT administration of rhHNS on Day 2. Patients will be discharged from the inpatient unit a minimum of 1 day following dosing with rhHNS and when deemed clinically stable by the Investigator.

The IT injections are to be administered 28 days (±7 days [groups 1 and 2]) and 14 days (±3 days [group 3]) apart. If a patient's IDDD becomes nonfunctional, it will be replaced so that the patient can remain on study. See Section 6.5 for a description on the replacement of a nonfunctional IDDD.

6.4 Cerebral Spinal Fluid Sample Procedure

A total of 10 mL of CSF will be obtained in two 5 mL aliquots prior to each injection for safety evaluation using the IDDD. A topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to CSF sampling. However, CSF will not be obtained if use of the IDDD is precluded, with the exception at the EOS visit, when it may be obtained by means of a lumbar puncture (LP). The performance of LP is at the discretion of the Investigator. An intracranial pressure (ICP) measurement will be obtained whenever a LP is performed.

If a lumbar puncture is to be performed, the patient will be anesthetized via general anesthesia with appropriate airway management. Once the patient is anesthetized, a lumbar puncture will be performed and a CSF sample will be obtained.

6.5 Intrathecal Administration of rhHNS

rhHNS will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive mild sedation to alleviate anxiety and/or to facilitate drug delivery.

Patients will then receive their appropriate dose of rhHNS via slow push/ injection over 2 to 5 minutes. Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during enzyme administration and through the next 24 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

If use of the IDDD is precluded on a scheduled day of dosing, the IDDD will be declared a failure; no study drug will be administered, nor CSF sample obtained on that visit. Unlike the HGT-SAN-055 study, no study drug will be administered by lumbar puncture in this extension study. Upon declaration of failure, the IDDD will be removed and the patient scheduled for re-implantation of a new IDDD (see Section 7.11) at the earliest convenience, so that the patient may remain on, or remain as close as possible, to his/her original IT rhHNS dosing schedule. Note: Patients will require 1 week of recovery time from time of re-implantation, during which time the IDDD cannot be used, this may result in a delay in the next scheduled dose of rhHNS. The patient will resume his or her original dosing schedule; no catch-up dosing will occur.

6.6 Method of Assigning Subjects to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with rhHNS. Patients will remain in the groups (1, 2, or 3) they were assigned to in Study HGT-SAN-055.

6.7 Blinding

Not applicable; this trial is not blinded.

6.8 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Reference List (WHODRL).

6.9 Restrictions

6.9.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than rhHNS or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.9.2 Fluid and Food Intake

Oral food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.9.3 Subject Activity Restrictions

There are no restrictions on patient activities in this study.

6.10 Treatment Compliance

rhHNS is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.11 Packaging and Labeling

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of rhHNS. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminum seal with a flip-off, plastic, tamper evident cap.

6.12 Storage and Accountability

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

6.13 Investigational Product Retention at Study Site

All rhHNS study drug delivered to an Investigator will be recorded and accounted for throughout the study. All rhHNS study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed after Sponsor approval per site policy after the study has been completed.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or legal guardian(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. The approximate maximum total blood, urine, and CSF volumes to be collected from each patient by the end of this study for safety assessments are presented in Table 7-1.

Table 7-1 Approximate Total Sample Volumes Collected Over the Duration of the Study From Each Patient by Group and Assay

	Groups 1 and 2	Group 3
Blood	290 mL	555 mL
Urine	530 mL	1,010 mL
CSF	480 mL	960 mL

Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory and/or Study Operations Manual.

7.2 Physical Examination

A physical examination of each patient will be performed as detailed in Appendix 1 Schedule of Events.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the baseline visit. If is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that same visit. See Section 7.9 for details. Note: Pressure-equalization tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) measurements will be taken once. All data will be recorded on the eCRF.

7.4 Head Circumference

Head circumference will be measured once. The data will be recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory and/or Study Operations Manual.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

7.7.2.1 Standard Serum Chemistry

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO2)
- Chloride (Cl)
- Creatinine
- Creatine kinase (CK) and subtypes
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

7.7.3 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.7.3.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory on urine samples:

- Macroscopic examination
- Microscopic examination of sediment
- pH

7.7.3.2 Urine Heparan Sulfate and Heparan Sulfate Derivatives

A urine sample will be collected for the determination of heparan sulfate and heparan sulfate derivatives and the analysis will be performed at Shire HGT laboratories. A urine sample from each visit will be reserved for possible, exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.4 Cerebrospinal Fluid Assessments

Cerebrospinal fluid (CSF) samples (10 ml in two 5 ml aliquots; labeled separately and processed according to the study operations manual) will be obtained from patients through an implanted IDDD. Should the IDDD become blocked or undergo mechanical complications, the CSF sample will not be obtained via lumbar puncture (LP), except when part of the EOS visit. The performance of LP is at the discretion of the Investigator. See Section 6.4 for further details.

CSF sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.4.1, 7.7.4.2, and 7.7.4.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites or protein or RNA may become available in the future (the samples maybe analyzed, if the assays are found applicable) and are thus not presently listed within this protocol.

7.7.4.1 CSF Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.4.2 CSF Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire HGT laboratories.

7.7.4.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of anti-rhHNS antibodies at Shire HGT laboratories.

7.7.4.4 CSF Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of MPS exploratory biomarkers at Shire HGT laboratories.

7.7.5 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual to be provided by Shire HGT.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded – see Section 6.4), prior to performing the MRI of the head, the ABR, the intracranial pressure (ICP), and the re-implantation of the IDDD (if applicable). See Appendix 1 for the Schedule of Events.

Note: the neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to co-operate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgement to initially estimate the extent of hearing loss (if any) during the initial physical examination. In this situation, specific evaluation of hearing loss will await examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will ask and offer the parent or guardian placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The auditory brainstem response (ABR) will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 MRI of the Head

The regional brain volume will be assessed through an MRI of the head. The patient will be under general anesthesia for this assessment. The central reading for MRI data, across all sites, will be completed at the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced so that the patient can remain on study. Procedures for implantation will be detailed in the device's Instructions for Use manual. The patient will be under general anesthesia for this procedure. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm device placement at the mid-thoracic level. A post-operative check of the IDDD will be performed on Day 7 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study. Drug can only be administered via the IDDD.

7.12 Intracranial Pressure Measurement

Intracranial pressure measurement (ICP) (centimeters of H2O) will be conducted per standard hospital practice. The measurement will be obtained whenever a LP is performed.

7.13 Dispensing Study Drug

rhHNS will be administered IT by means of an IDDD to patients in Dose Groups 1 and 2 on Day 2 (±2 days) of Week 1 of each treatment month and to patients in Dose Group 3 on Day 2 (±2 days) of Weeks 1 and 3 of each treatment month.

The patient may be mildly sedated for this procedure; rhHNS will be administered over 2 to 5 minutes. Please see Section 6.5 if the IDDD is not functioning.

The patient must not receive aspirin, non-steroidal anti-inflammatory medications, or medications that affect clotting within 1 week prior to each IT injection.

7.14 Pharmacokinetic Assessments

Pharmacokinetic assessments will not be included in this study.

7.15 Neurological Examination

A neurological examination to monitor CNS changes in patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

7.16 Serum Anti-rhHNS Antibody, Heparan Sulfate and Heparan Sulfate Derivative Determination

Blood samples will be collected prior to rhHNS injection and evaluated at Shire HGT laboratories for the determination of anti-rhHNS antibodies, heparan sulfate and heparan sulfate derivatives. Samples will be reserved for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two 5 mL blood samples will be collected from each patient at each designated time point. One 5 mL sample will be collected in a tube intended for serum specimens, while the second sample will be collected in a tube intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory and or Study Operations Manual.

7.17 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-2 and Table 7-3, respectively. See Appendix 3 for details on these assessments.

Table 7-2 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor	0 to 42 months: Bayley Scales of Infant Development-III (BSID-III) [23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II) [24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2) [25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III) [23]

Table 7-2 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition [26]

Table 7-3 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

Developmental or Cognitive Domain(s)	Sanfilippo Specific Assessments
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[4]

7.18 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's patients/legal guardian.

7.19 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.19.1, 7.19.2, and 7.19.3.

7.19.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study.

The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age

7.19.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being

7.19.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/guardian's life.

7.20 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHODRL.

7.21 Adverse Events

7.21.1 Adverse Events Assessments

Adverse events will be monitored continuously throughout the study from the time the patient, patient's parent/legal guardian signs the informed consent/assent (if applicable) until the safety follow-up contact or until the event has resolved or stabilized, or an outcome is reached, whichever comes first.

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

7.21.2 Definitions of Adverse Events and Serious Adverse Events

7.21.2.1 Adverse Event

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed, any adverse event prior to the start of study drug must be reported.

AEs include:

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

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

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

All adverse events should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for adverse events associated with intrathecal injections of rhHNS. In general, these adverse events can be classified as follows:

- Adverse events due to systemic exposure to rhHNS caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of rhHNS to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related adverse events.

Note: the classification of potential adverse events and the examples presented below are based on purely theoretical considerations and/or published literature as there is no human experience with intrathecal rhHNS therapy to date.

POTENTIAL ADVERSE EVENTS: INTRATHECAL RHHNS

Adverse Events Due To Systemic Exposure To rhHNS

Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

Adverse Events Related to the Direct Delivery of rhHNS to the CNS Through Intrathecal Administration

Examples of adverse events observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory parathesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time.

Potential Adverse Events: IDDD -Related Adverse Events

Examples of adverse events related to the insertion or use of an IDDD include, but are not limited to, the following: catheter disconnection or fracture, erosion of portal/catheter through the skin, fibrin sheath formation around catheter tip, hematoma, implant rejection, malposition of catheter, migration of portal/catheter, occlusion of portal/catheter, portal site or subcutaneous tract infection, and sepsis.

In addition, there are risks associated with intraspinal access, which include the following: cerebrospinal fluid leaks, dura mater or epidural vein perforation, epidural or intrathecal space infection (which could result in meningitis), inadvertent epidural placement, pain on injection, and spinal cord or nerve injury.

7.21.2.2 Serious Adverse Event

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

- Death
- Is life-threatening
- Requires inpatient hospitalization
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity

- A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 5) If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-4. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-4 Adverse Event Severity

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

Relationship of an adverse event or serious adverse event to study medication is to be determined by the Investigator based on the definitions in Table 7-5:

Table 7-5 Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	Unrelated to study drug.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the medication, follows a known or suspected response pattern to the medication, is confirmed by improvement upon stopping the medication (dechallenge) and reappears upon repeated exposure (rechallenge).

Table 7-5 Adverse Event Relatedness

Relationship to Product(s)	Definition
	Note that this is not to be construed as requiring re-exposure of the patient to study drug; however, the determination of definitely related can only be used when recurrence of event is observed.

7.21.3 Procedures for Recording and Reporting Adverse Events

7.21.3.1 Reporting Serious Adverse Events

Any SAE, regardless of relationship to study medication, which occurs in a patient after informed consent, should be recorded by the clinical site on an SAE form. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study drug or device. The Investigator will promptly supply all information identified and requested by the Sponsor (or contract research organization [CRO]) regarding the SAE.

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

Shire Pharmacovigilance and Risk Management Department:

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

AND

Shire HGT Medical Monitor: [redacted] MD

[redacted]

FAX: [redacted](USA)

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

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

If an SAE is assessed as severe and unexpected, or life-threatening, contact:

[redacted] MD
[redacted]
Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139, USA
Telephone: [redacted]
Fax: [redacted] (USA)
Mobile: [redacted]

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/ MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

7.21.3.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. In addition, the relationship of each AE to study medication must be recorded.

7.21.3.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results. The Investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire HGT Medical Monitor (see Section 7.21.3.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient. The Investigator or other physician in attendance in such an emergency must contact the Shire HGT Medical Monitor as soon as possible.

The Investigator, along with the Shire HGT Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.22 Pregnancy

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

7.23 Removal of Subjects from the Trial or Study Drug

The patient's parent or legal guardian acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If for any reason the patient refuses treatment during the study, the patient will be withdrawn from the study, and the reason for refusal will be documented on the eCRF. Reasonable efforts will be made to monitor the patient for AEs following such discontinuation. Such efforts will be documented in the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized guardian may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.

- Clinically problematic intubations or extubations which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.

If a patient or the patient's legal guardian(s), acting on behalf of the patient, discontinues participation in the study, or the patient is discontinued by the Investigator, the Patient Completion/Discontinuation Case Report Form (eCRF) describing the reason for discontinuation must be completed. Any adverse events (AE's) experienced up to the point of discontinuation must be documented on the AE eCRF. If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.24 Other Study Procedures

This section is not applicable.

7.25 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers will provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 (patients who were dosed monthly) or Week 28 (patients who were dosed every other week) and completed the End of Study evaluations will be eligible for enrollment in this open-label extension study. Informed consent will be provided by the patient's parent(s)/legal guardian(s) prior to start of extension study procedures.

If there are no safety concerns, patients who were previously treated with intrathecal rhHNS in Study HGT-SAN-055 and elect to continue rhHNS treatment will continue receiving monthly (Groups 1 and 2) or EOW (Group 3) intrathecal rhHNS in this extension study, as described in Appendix 1 Schedule of Events.

8.1 Screening Visit/Baseline Visit

All Screening assessments for this study are to have been performed during the Week 26 (Groups 1 and 2) or Week 28 (Group 3) (30 [±7] days after the last rhHNS administration) EOS procedures in HGT-SAN-055. If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, the assessments detailed in this Screening visit are not required to be repeated. The Baseline Visit for this study will be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal rhHNS dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Serum chemistry
- Urinalysis
- Neurological examination (performed prior to the administration of anesthesia)
- Neurodevelopmental assessments (performed prior to the administration of anesthesia
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
  - ABR
  - MRI of the head
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Urine heparan sulfate and heparan sulfate derivatives

- Serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Monthly, Weekly Assessments

Patients in Dose Groups 1 and 2 will receive rhHNS IDDD monthly, on Week 1, Day 2 (±2 days). Patients in dose Group 3 will receive rhHNS EOW, on Weeks 1 and 3, Day 2 (±2 days).

8.2.1 Week 1 (Groups 1 and 2); Week 1 and 3 (Group 3)

8.2.1.1 Day 1 (Pre-treatment) Assessments

- Informed consent (Week 1, Month 1 only) prior to study HGT-SAN-067 study procedures
- Physical examination
- Height and weight
- Vital signs
- Hematology
- Serum Chemistry
- Urinalysis
- Neurological Examination (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Concomitant Medications, Therapies, and Procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or Screening) assessments were performed within 7 days of first intrathecal rhHNS treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED ONLY AT MONTHS 12, 24, 36, AND 48

- Head circumference
- Visual and hearing assessments
- Urine Heparan Sulfate and Heparan Sulfate Derivatives (Group 3: obtained only at first week of each treatment month)
- Serum Heparan Sulfate and Heparan Sulfate Derivatives (Group 3: obtained only at first week of each treatment month)

- Anti-rhHNS antibody testing
- Auditory Brainstem Response (ABR)
- MRI of the head
- Full neurodevelopmental testing (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and IDDD Injection of rhHNS

- Physical examination
- ECG (performed following IT study drug injection)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- rhHNS IT injection (Day 2 ±2 days)
- neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

8.2.1.3 Day 3 (Post IT Dose) Assessments

Patients will be discharged when deemed clinically stable by the Investigator.

- Vital signs
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

8.3 End of Study/ Early Termination Procedures

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of rhHNS. Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the end of study procedures at time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: scheduled removal of the IDDD will be required at study completion with sedation or anesthesia, as required.

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing

- ECG
- Vital signs
- Hematology
- Serum Chemistries
- Urinalysis
- Urine Heparan Sulfate and Heparan Sulfate Derivatives
- Serum Heparan Sulfate and Heparan Sulfate Derivatives
- Anti-rhHNS antibody testing
- Auditory Brainstem Response (ABR)
- MRI of the head
- CSF sample collection
- Neurological examination
- Full neurodevelopmental testing
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

8.4 Safety Follow-up Visit (by Telephone)

Patients who complete the study will have a safety follow-up visit 30 Days (±7 days)

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the safety follow-up visit at the time of discontinuation. Participation in these procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study.

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire HGT or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of rhHNS in patients with Sanfilippo syndrome type A (MPS IIIA). The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg per month, 45 mg per month and 45 mg every other week) with respect to demographic and baseline characteristics, efficacy variables and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time.

All hypothesis tests will be 2-sided and will be performed at the 0.05 level. Hypothesis testing will be viewed as exploratory. Any resulting p-values will not be regarded as a firm support for conclusions, but rather suggestive of areas of examination in future studies. In general, variables will be quantified as a change from the baseline value. The null hypothesis will be that there is no difference in the change from baseline between dose groups. Note that the baseline visit for this study will be the first day the patient received his/her IT dose of rhHNS in study HGT-SAN-055.

The primary objective of this trial is to assess the long term safety of rhHNS administration via a surgically implanted intrathecal drug delivery device (IDDD). Hence an extensive safety assessment will be performed. The safety analyses will consist of all enrolled patients. To evaluate safety, adverse experiences will be tabulated by dose group. Vital signs, electrocardiograms, serum and CSF components and chemistries, hematology, and urinalysis safety monitoring will be listed for each patient and abnormal values will be flagged. In addition, anti-rhHNS antibodies (in CSF and serum) will also be listed. No formal statistical tests will be performed on the safety parameters.

10.2 Determination of Sample Size

Since this is an extension study, sample size is determined by the number of patients who completed HGT-SAN-055 (maximum of 12 patients) and enrolled in this study

10.3 Analysis Populations

The analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. Both safety and efficacy analyses would be performed using the above mentioned population.

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew, by dose group. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of treatment-emergent adverse events, due to study drug and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients will be included in the safety analysis. Patients will be grouped according to the actual dose received.

No formal statistical test will be performed in the safety evaluations. Vital sign measurements, clinical chemistry, and hematology safety monitoring will be listed for each patient, and abnormal values will be flagged. These will also be summarized at each time point, including change from baseline.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 9.0 or later. In all cases (with the exception of device-related events), adverse event summaries will be based on all adverse event recorded beginning on Study Day 1 (treatment-emergent AEs).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in system organ class, and having each individual adverse event. Note that in any given category (eg, system organ class) a patient will only be counted once. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication.

Adverse events that occur up to 30 days after the last dose of study drug will be considered "on-treatment". Adverse events which are deemed probably or possibly related to the device will be summarized by dose group and overall.

Laboratory data will be listed by patient and dose group. Patients with newly occurring abnormalities outside the normal range will be flagged and listed separately and summarized. Mean change from baseline values or shift tables will also be provided by dose group at each visit.

Vital signs data will be listed by patient and dose group. Furthermore, mean changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

ECG assessments will be listed by patient and dose group. Mean changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.1.2 Clinical Laboratory Evaluations

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis) results will be presented in summary tables by evaluation visit using number of patients (n), mean, median, standard deviation, minimum, and maximum. Changes from baseline will be summarized for each post-baseline visit. The number of patients with clinically significant laboratory results or abnormal results during the study period will be presented in shift tables.

For the laboratory measurements, shift tables will be presented in terms of Low (L), Normal (N), High (H), Missing (M). High and Low measurements will be based on reference ranges provided by the laboratory at the study site.

Clinical laboratory results will also be presented in data listings.

10.6.1.3 Anti-rhHNS Antibody Formation

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by assay methodology used to identify antibodies, number and percentage of positive and negative specimens by evaluation visit and/or study week, and number and percentage of positive and negative specimens overall. These results will also be presented in data listings.

10.6.2 Secondary Analysis

10.6.2.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of rhHNS administration on QoL measures will be examined by presenting mean change from baseline across dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.2.2 Pharmacodynamic Analyses

To determine the effects of rhHNS administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparin sulfate reduction (in CSF and urine) will be examined using mean change and the corresponding 95% confidence interval. The concentration of inflammatory cytokines in serum and CSF will also be examined. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

The planned analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki (2008).

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol. Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. On-site review of the eCRF's for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the electronic clinical report form (eCRF). The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

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

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire HGT. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire HGT.

11.8 Data Monitoring Committee

There will be no data monitoring committee for this study.

11.9 Protocol Violations/Deviations

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

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 9.0 or later. Concomitant medication will be coded using WHODRL. Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire HGT and the Investigators. In addition, a decision on the part of Shire HGT to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

12 REFERENCE LIST

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Appendix 1 Schedule of Events

Table 1 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Groups 1 and 2)

		Week 1 Each Treatment Month					
Assessment	**Screening/ Baseline Visit[i]**	**Pre-Tx Day 1[a, l]**	**IT administration Day 2**	**Day 3[d]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Informed Consent/Enrollment		●					
Physical Examination	●	●	●			●	
Height and Weight	●	●				●	
Head Circumference	●				●	●	
Visual and Hearing Assessment					●	●	
ECG	●		●[b]			●	
Vital Signs	●	●	●	●		●	
Hematology	●	●				●	
Serum Chemistry	●	●				●	
Urinalysis	●	●				●	
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Serum Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[j]	●				●	●	
Auditory Brainstem Response (ABR)	●				●	●	
MRI of the Head	●				●	●	
CSF Sample Collection[k]	●		●[c]			●[c]	
rhHNS administration[g]			●				
Neurological Examination	●	●	●	●		●	
Full Neurodevelopmental Testing	●				●	●	
Children's Sleep Habits Rating Scale	●				●	●	
Child Health Questionnaire-50	●				●	●	
Child Health Questionnaire-87	●				●	●	
Infant Toddler QOL Questionnaire	●				●	●	

Table 1 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Groups 1 and 2)

		Week 1 Each Treatment Month					
Assessment	**Screening/ Baseline Visit[i]**	**Pre-Tx Day 1[a, l]**	**IT administration Day 2**	**Day 3[d]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Concomitant Medications, Therapies, and Procedures	●	●	●	●		●	●
Adverse Event Monitoring	●	●	●	●		●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; ECG = electrocardiogram; MRI = Magnetic resonance imaging; TX = treatment;

a Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

b ECG to be performed following administration of study drug.

c A total of 10 mLs of CSF will be obtained in two 5 mL aliquots (labeled separately – process according to study operations manual). An attempt will be made to obtain CSF sample via the IDDD prior to each administration of rhHNS and at the End of Study visit. If it is not possible to obtain CSF using the IDDD, the IDDD will be replaced. See Section 6.4 for details.

d Patients will be discharged when deemed clinically stable by the Investigator.

e Specimens collected once a month, at Day 1 of the first treatment week.

f All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

g If a patient's IDDD becomes nonfunctional or infected; it will be replaced so that the patient can remain on study. See Section 6.5.

h A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

i Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled rhHNS IT dose.

j Blood sample drawn before IT injection of rhHNS.

k CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

Table 2 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Group 3)

		Week 1 and 3 Each Treatment Month					
Assessment	**Screening/Baseline Visit[i]**	**Pre-Tx Day 1[a]**	**IT administration Day 2**	**Day 3[d,]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Informed Consent/Enrollment		●					
Physical Examination	●	●	●			●	
Height and Weight	●	●				●	
Head Circumference	●				●	●	
Visual and Hearing Assessment					●	●	
ECG	●		●[b]			●	
Vital Signs	●	●	●	●		●	
Hematology	●	●				●	
Serum Chemistry	●	●				●	
Urinalysis	●	●				●	
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Serum Heparan Sulfate and Heparan Sulfate Derivatives	●				●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[j]	●				●	●	
Auditory Brainstem Response (ABR)	●				●	●	
MRI of the Head	●				●	●	
CSF Sample Collection[k]	●		●[c]			●[c]	
rhHNS administration[g]			●				
Neurological Examination	●	●	●	●[j]		●	
Full Neurodevelopmental Testing	●				●	●	
Children's Sleep Habits Rating Scale	●				●	●	
Child Health Questionnaire-50	●				●	●	
Child Health Questionnaire-87	●				●	●	
Infant Toddler QOL Questionnaire	●				●	●	

Table 2 Study Assessments for Patients Who Have Received 6 Months of Treatment With rhHNS (Study HGT-SAN-055) (Dose Group 3)

		Week 1 and 3 Each Treatment Month					
Assessment	**Screening/Baseline Visit[i]**	**Pre-Tx Day 1[a]**	**IT administration Day 2**	**Day 3[d,]**	**12, 24, 36, and 48 months**	**End of Study[f]**	**Safety Follow-up[h]**
Concomitant Medications, Therapies, and Procedures	●	●	●	●		●	●
Adverse Event Monitoring	●	●	●	●		●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; ECG = electrocardiogram; MRI = Magnetic resonance imaging ; TX = treatment;

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] A total of 10 mLs of CSF will be obtained in two 5 mL aliquots (labeled separately – process according to study operations manual). An attempt will be made to obtain CSF sample via the IDDD prior to each administration of rhHNS and at the End of Study visit. If it is not possible to obtain CSF using the IDDD, the IDDD will be replaced. See Section 6.4 for details.

[d] Patients will be discharged when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced so that the patient can remain on study. See Section 6.5.

[h] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[i] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled rhHNS IT dose.

[j] Blood sample drawn before IT injection of rhHNS.

[k] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

Appendix 2 Sample Neurological Exam

☐ Not Done, Please provide reason: _____

Exam date: _____ (Day/Mon/Year) Name of Examiner: _____

Overall neurological impression	☐ Normal ☐ Abnormal

Please mark normal, abnormal, or unable to determine for each item listed. If any abnormalities are found, please specify the findings in the space provided.

Items	Status	Please describe abnormalities
Observation and mental status		
Alertness	☐ Normal ☐ Abnormal ☐ Not Done	
Interaction with care taker	☐ Normal ☐ Abnormal ☐ Not Done	
Activity level	☐ Normal ☐ Abnormal ☐ Not Done	
Involuntary movements	☐ Absent ☐ Present ☐ Not Done	
Cranial nerves		
Pupillary reaction to light	☐ Normal ☐ Abnormal ☐ Not Done	
Extra ocular movements	☐ Normal ☐ Abnormal ☐ Not Done	
Eye closure	☐ Normal ☐ Abnormal	

Items	Status	Please describe abnormalities
	☐ Not Done	
Facial symmetry	☐ Normal ☐ Abnormal ☐ Not Done	
Coordination/Sensory		
Rapid finger tapping	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Finger to nose	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Stand on one foot	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Hop on one foot	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Romberg	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Deep tendon reflexes		
Biceps	☐ Normal ☐ Abnormal ☐ Not Done	
Patellar	☐ Normal ☐ Abnormal ☐ Not Done	
Ankle	☐ Normal	

Items	Status	Please describe abnormalities
	☐ Abnormal ☐ Not Done	
Deep tendon reflexes (continue)		
Ankle clonus	☐ Absent ☐ Present ☐ Not done	
Gait		
Natural walking	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Straight line walking	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Tandem walking	☐ Normal ☐ Abnormal ☐ Unable to Perform ☐ Not Done	
Other		
Specify: _____	☐ Normal ☐ Abnormal	
Specify: _____	☐ Normal ☐ Abnormal	
Specify: _____	☐ Normal ☐ Abnormal	

Items	Status	Please describe abnormalities
Specify: _____	☐ Normal ☐ Abnormal	

Appendix 3 Neurodevelopmental and Behavioral Assessments

Table 3-1 and Table 3-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table 3-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table 3-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[4]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child’s abilities to perform certain skills (sitting, walking, and talking). However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns.

For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III)[23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]

Purpose:

The KABC-II measures a child’s cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery’s results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient’s assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 4 Investigator's Signature

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

Study Number: HGT-SAN-067

Final Date: 21 June 2010

Amendment 1 Date: 27 January 2011

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

Signed: [redacted] Date: [redacted]

[redacted] Dr. [redacted]
[redacted]
[redacted]
[redacted]
The Netherlands
[redacted]

Signed: [redacted] Date: [redacted]

[redacted] MD
[redacted]

Shire HGT
700 Main Street
Cambridge, MA 01239

[redacted]

Appendix 5 Summary of Changes for Amendment 1

Clinical protocol HGT-SAN-067 has been revised from the previous version (original protocol, 21 June 2010) to clarify that the study duration will be 4 years.

In addition, one administrative change was made to the protocol; the title of the National Cancer Institute grading scale version 3.0 title was corrected: The National Cancer Institute Common **Toxicity Criteria (NCI CTC)** Version 3.0 was modified to correctly state The National Cancer Institute Common **Terminology Criteria for Adverse Events** (CTCAE) Version 3.0.

The amendment number is 1.

The change relative to the original protocol (21 June 2010) has been made in the protocol and is summarized below by section number; new or additional text is indicated in bold and deleted text is indicated as strikethrough below. Other sections affected by the same change are listed below each change.

Change: The text was modified to clarify that the study duration will be 4 years.
Section impacted by this change: Section 4.3 Study Duration and Dates
Modified Text: The study duration will be ~~a maximum duration of~~ 4 years ~~of rhHNS treatment or until rhHNS is commercially available, the patient discontinues from the study, the Sponsor stops the study, or the Sponsor discontinues the development of rhHNS. Study completion will be defined as the time at which a patient completes 4 years of rhHNS treatment (including participation in study HGT-SAN-055), or transitions to commercially available rhHNS or discontinues from this study for other reasons.~~
Other sections affected by the same change: Synopsis

Appendix 6 The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
Medical Monitor:	[redacted] MD, [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421 USA

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS)

Name of Active Ingredient:

rhHNS

Name of Inactive Ingredient:

N/A

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

Study Phase: I/II

Study Objectives:

Primary Objective:

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received rhHNS via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy in study HGT-SAN-067.

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

The primary endpoint of this study is:

- To determine the long-term safety of intrathecal rhHNS administration, as measured by the adverse events (type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms (ECG), cerebrospinal fluid (CSF), chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in CSF and serum.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and/or CSF, and if possible, in serum and/or plasma.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR, Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of rhHNS via an IDDD in patients with 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 rhHNS treatment. Patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first rhHNS dose in HGT-SAN-067.

Enrolled patients will check in to the study center 1 day before each of the scheduled rhHNS dosing days for safety assessments (designated Day 1). If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least 8 hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out. A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study). Note: X-rays may be performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy may be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055).

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria will be applied and will be based on the types and severity of adverse events (AEs) reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of rhHNS (ie, Month 55). The EOS procedures will include 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, and MRI.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of rhHNS. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the protocol appendix which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of rhHNS, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), rhHNS will be administered via lumbar puncture (LP). Study drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with rhHNS.

Test Product; Dose; and Mode of Administration:

Recombinant human heparan N-sulfatase (rhHNS) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly).

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.

2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of rhHNS in the HGT-SAN-055 study.
4. The Patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Subjects will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.
3. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

Duration of Treatment:

The study duration will be 4 years.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods:

The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval around the mean will be presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 2: 13 January 2012

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CNS	central nervous system
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CO_2	carbon dioxide
CRO	contract research organization
CRIM	cross-reacting immunologic material
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score

GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonisation
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MABC-2	Movement Assessment Battery for Children, Second Edition
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
QoL	quality of life

PE	pressure-equalization
Q4W	Every 4 weeks
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UK	United Kingdom
US	United States
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)
WHO-DD	WHO Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. The patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is a lysosomal storage disease (LSD) caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. MPS IIIA results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtypes A and B similar in prevalence, accounting for approximately 90% of all cases of MPS III.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1,2,3] In summary, MPSIIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4,5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5,6,7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8] A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the CSF via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11,12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the rhHNS clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an IDDD due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13,14,15,16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L-Idurunonidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358). This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse events monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire HGT-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of rhHNS in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, rhHNS was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of rhHNS leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of rhHNS to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 µg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 µg dose given IT every-other-week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mg rhHNS given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, the highest dose of rhHNS was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no rhHNS-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene. In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs, rhHNS (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of rhHNS into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg rhHNS resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis, astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg rhHNS per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of rhHNS (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg rhHNS was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 Study Rationale

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

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will continue to receive rhHNS at the same dose and schedule as they received in Study HGT-SAN-055. The dose for each group will remain unchanged during this study unless safety and/or efficacy analyses of HGT-SAN-055 data indicate otherwise. Meaningful composite analysis of the optimum dose and regimen will come only after all 3 dose groups complete the entire HGT-SAN-055 study.

Please refer to the current edition of the rhHNS Investigator's Brochure for further information.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

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

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

To determine the long-term safety of IT rhHNS administration, as measured by adverse events (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms (ECG), cerebrospinal fluid (CSF), chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

3.2 Secondary Endpoints

The secondary endpoints of this study are 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, quality of life (QoL) questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in CSF and serum.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine, plasma, and serum.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), (also know as Brainstem Auditory Evoked Potentials).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of intrathecal (IT) administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of rhHNS via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted rhHNS treatment. Patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

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

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 patient received their first IT dose of rhHNS in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first rhHNS dose in HGT-SAN-067.

Enrolled patients will check in to the study center 1 day before each of the scheduled rhHNS dosing days for safety assessments (designated Day 1). If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least 8 hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out.

A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055).

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 electronic case report forms (eCRFs). Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of rhHNS (ie, Month 55). The EOS procedures will include 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, and MRI. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of rhHNS. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to protocol Appendix 3 which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. A maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of rhHNS, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, rhHNS will be administered via lumbar puncture (LP). Drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of rhHNS via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT rhHNS administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with rhHNS in the HGT-SAN-067 study.

4.3 Study Duration and Dates

The study duration will be 4 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue rhHNS treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of rhHNS in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

Recombinant human heparin N-sulfatase (rhHNS) drug product formulation is a sterile solution for injection in single-use vials for intrathecal (IT) administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, 0.005% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.

6.1.2 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

rhHNS for IT administration will be provided by Shire HGT. rhHNS will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will receive the same dose of rhHNS they received in Study HGT-SAN-055:

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

6.2.1 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT rhHNS dosing for safety assessments, designated Day 1, on each rhHNS treatment week, and if no safety concerns exist, will receive IT administration of rhHNS on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the Investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least 8 hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details). In the event of a non-functional IDDD, rhHNS may be administered by LP, for up to 5 successive months (see Section 6.2.4).

6.2.2 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for safety evaluation and biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the Study Operations Manual. CSF opening pressure will be measured whenever a LP is performed, and at the time of IDDD revision (partial or replacement). Additional CSF samples may be taken during this time.

6.2.3 Intrathecal Administration of rhHNS

rhHNS will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive rhHNS via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 8 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.2.4). The investigation and management of a malfunctioning IDDD is detailed in Appendix 3. If the failure is mechanical, partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.2.4 Administration of rhHNS via Lumbar Puncture

In the event of a non functional IDDD, rhHNS may be administered by LP, for up to 5 successive months. The performance of a LP is at the discretion of the Investigator.

If a LP is to be performed, the patient may require general anesthesia with appropriate airway management. Once the patient is anesthetized, a LP will be performed and a CSF sample will be obtained. Some cases may be managed with conscious sedation, if this is considered by the investigator to be adequate for the safe and expeditious performance of a LP.

6.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with rhHNS. Patients will remain in the groups (1, 2, or 3) they were assigned to in Study HGT-SAN-055.

6.4 Blinding

Not applicable; as this trial is not blinded.

6.5 Concomitant Therapy

All non-protocol treatments and procedures that occur from the time of informed consent (and assent, if applicable) through the safety follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the electronic case report form (eCRF). Concomitant therapy includes medications (including Genistein), therapies/interventions administered to patients, and medical/surgical procedures performed on the patients.

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 WHO Drug Dictionary (WHO-DD).

6.6 Restrictions

6.6.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than rhHNS or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.6.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.6.3 Patient Activity Restrictions

There are no restrictions on patient activity in this study.

6.7 Treatment Compliance

rhHNS is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.8 Packaging and Labeling

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of rhHNS. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminum seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9 Storage and Accountability

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

6.10 Investigational Product Retention at Study Site

All rhHNS study drug delivered to an Investigator will be recorded and accounted for throughout the study. All rhHNS study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory and/or Study Operations Manual.

7.2 Physical Examination

A physical examination of each patient will be performed as detailed in Appendix 1 Schedule of Events.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.10). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory and/or Study Operations Manual.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.8 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.8.1.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.8.1.2 Urine Heparan Sulfate and Heparan Sulfate Derivatives

A urine sample will be collected for the determination of heparan sulfate and heparan sulfate derivatives and the analysis will be performed at Shire HGT or designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.8.2 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.8.2.1, 7.8.2.2, and 7.8.2.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or RNA may become used as they become available in the future.

7.8.2.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.8.2.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire HGT laboratories.

7.8.2.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of anti-rhHNS antibodies at Shire HGT or Shire HGT designated laboratories.

7.8.2.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of MPS exploratory biomarkers at Shire HGT laboratories.

7.8.3 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual to be provided by Shire HGT.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.9 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.10 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the auditory brainstem response (ABR) (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.11 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. Management details are provided in Appendix 3. Procedures for implantation are detailed in the device's Instructions for Use Manual and in the training materials provided by Shire HGT. The patient will be under general anesthesia for this procedure. The CSF opening pressure will be recorded when the intrathecal space is first entered at the time of the IDDD re-implantation. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly (correct orientation of the locking device on the access port), and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the Study Operations Manual). A post-operative check of the IDDD and incision will be performed on Day 4 following surgery.

X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision or replacement is done.

7.14 Dispensing Study Drug

rhHNS will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. rhHNS will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, rhHNS may be administered via LP. See Section 6.2.4 for details.

7.15 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.16 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

7.17 Anti-rhHNS Antibody, Heparan Sulfate, and Heparan Sulfate Derivative Determination

Blood samples will be collected and evaluated at Shire HGT laboratories for the determination of anti-rhHNS antibodies, and plasma and serum heparan sulfate and heparan sulfate derivatives. Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual.

7.18 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.19 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.20 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.20.1, 7.20.2, and 7.20.3.

7.20.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age

7.20.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being

7.20.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.21 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.22 Adverse Events

7.22.1 Definitions of Adverse Events and Serious Adverse Events

7.22.1.1 Adverse Event

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

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

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

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

All adverse events should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of rhHNS. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to rhHNS caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of rhHNS to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs.

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal rhHNS therapy to date.

POTENTIAL ADVERSE EVENTS: INTRATHECAL rhHNS

Adverse Events Due To Systemic Exposure To rhHNS

Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

POTENTIAL ADVERSE EVENTS: INTRATHECAL RECOMBINANT HUMAN HEPARAN N-SULFATASE

Adverse Events Due to Systemic Exposure to rhHNS

Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

Adverse Events Related to the Direct Delivery of rhHNS to the CNS through Intrathecal Administration

Examples of adverse events observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory parathesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time.

POTENTIAL ADVERSE EVENTS: IDDD-RELATED ADVERSE EVENTS

Examples of adverse events related to the insertion or use of an IDDD include, but are not limited to, the following: catheter disconnection or fracture, erosion of portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, malposition of catheter, migration of portal/catheter, occlusion of portal/catheter, portal site or subcutaneous tract infection, and sepsis.

In addition, there are risks associated with intraspinal access, which include the following: cerebrospinal fluid leaks, dura mater or epidural vein perforation, epidural or intrathecal space infection (which could result in meningitis), inadvertent epidural placement, pain on injection, and spinal cord or nerve injury.

7.22.1.2 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3.

The severity of all AEs/SAEs should be recorded on the appropriate eCRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3 Adverse Event Severity

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

Relationship of an adverse event or serious adverse event to study medication is to be determined by the Investigator based on the definitions in Table 7-4:

Table 7-4 Adverse Event Relatedness

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

7.22.2 Procedures for Recording and Reporting Adverse Events

7.22.2.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire HGT Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study procedure. The Investigator will promptly supply all information identified and requested by the Sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device or procedure.

The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted](UK) OR
United States FAX: [redacted]
Email: [redacted]
AND
Shire HGT Medical Monitor:
FAX: [redacted](USA)

The Investigator may also call the Medical Monitor directly (optional):

Shire HGT Medical Monitor: [redacted] MD
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted](24 hour access)
Email: [redacted]
AND
Clinical Project Manager CC'd: [redacted]

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

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

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

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication

7.22.2.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. In addition, the relationship of each AE to study medication must be recorded.

7.22.2.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The Investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire HGT Medical Monitor (see Section 7.22.2.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The Investigator or other physician in attendance in such an emergency must contact the Shire HGT Medical Monitor as soon as possible.

The Investigator, along with the Shire HGT Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.23 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered possibly, probably, or definitely related to study drug, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered possibly, probably, or definitely related to the study drug by the sponsor, then the site will be instructed to halt further rhHNS administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.24 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of rhHNS throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of rhHNS. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a pregnancy test is positive the patient will be discontinued from the study, and the Investigator must contact the Shire HGT Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.25 Removal of Subjects from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.26 Other Study Procedures

This section is not applicable.

7.27 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first rhHNS dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last rhHNS administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of rhHNS in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal rhHNS dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
  - Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
  - Auditory Brainstem Response (ABR)
  - MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments (performed prior to the administration of anesthesia
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments

Patients will receive rhHNS IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection. Note: Patients will not receive study drug if the pre-dose CSF contains >100 WBC per cubic millimeter.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs
- Hematology
- Serum chemistry
- Urinalysis
- Pregnancy testing (applicable females only)
- Neurological examination (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal rhHNS treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, AND 54

- Head circumference
- Visual and hearing assessments
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and /or serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR
- MRI of the head
- Full neurodevelopmental testing (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of rhHNS

Patients may be discharged from the clinical site 8 hours after dosing, if deemed stable by the Investigator.

- Physical examination
- ECG (performed following IT study drug injection)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- rhHNS IT injection (Day 2 ±2 days)
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

8.3 End of Study/Early Termination Procedures: Month 55

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of rhHNS. Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Scheduled removal of the IDDD will be required at study completion with sedation or anesthesia, as required.

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG

- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- Auditory Brainstem Response (ABR)
- MRI of the head
- CSF sample collection
- Neurological examination
- Full neurodevelopmental testing
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

All patients who discontinue the study early will have their IDDD removed.

Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 56

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire HGT or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of rhHNS in patients with Sanfilippo syndrome type A (MPS IIIA). The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time.

All hypothesis tests will be 2-sided and will be performed at the 0.05 level. Hypothesis testing will be viewed as exploratory. Any resulting p-values will not be regarded as a firm support for conclusions, but rather suggestive of areas of examination in future studies. In general, variables will be quantified as a change from the baseline value. The null hypothesis will be that there is no difference in the change from baseline between dose groups. Note that the baseline visit for this study will be the first day the patient received his/her IT dose of rhHNS in study HGT-SAN-055.

The primary objective of this trial is to assess the long term safety of rhHNS administration via a surgically implanted intrathecal drug delivery device (IDDD). Hence an extensive safety assessment will be performed. The safety analyses will consist of all enrolled patients. To evaluate safety, adverse experiences will be tabulated by dose group. Vital signs, electrocardiograms, serum and CSF components and chemistries, hematology, and urinalysis safety monitoring will be listed for each patient and abnormal values will be flagged. In addition, anti-rhHNS antibodies (in CSF and serum) will also be listed. No formal statistical tests will be performed on the safety parameters.

10.2 Determination of Sample Size

Since this is an extension study, sample size is determined by the number of patients who completed HGT-SAN-055 (maximum of 12 patients) and elected to continue treatment with rhHNS in this study

10.3 Analysis Populations

The analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. Both safety and efficacy analyses would be performed using the above mentioned population.

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew, by dose group. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of adverse events, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients will be included in the safety analysis. Patients will be grouped according to the actual dose received.

No formal statistical test will be performed in the safety evaluations. Vital sign measurements, clinical chemistry, and hematology safety monitoring will be listed for each patient, and abnormal values will be flagged. These will also be summarized at each time point, including change from baseline.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in system organ class, and having each individual adverse event. Note that in any given category (eg, system organ class) a patient will only be counted once. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication.

Adverse events that occur up to 30 days after the last dose of study drug will be considered "on-treatment". Adverse events which are deemed probably, possibly, or definitely related to the device will be summarized by dose group and overall.

Laboratory data will be listed by patient and dose group. Patients with newly occurring abnormalities outside the normal range will be flagged and listed separately and summarized. Mean change from baseline values or shift tables will also be provided by dose group at each visit.

Vital signs data will be listed by patient and dose group. Furthermore, mean changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

Electrocardiograph assessments will be listed by patient and dose group. Mean changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.1.2 Clinical Laboratory Evaluations

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis) results will be presented in summary tables by evaluation visit using number of patients (n), mean, median, standard deviation, minimum, and maximum. Changes from baseline will be summarized for each post-baseline visit. The number of patients with clinically significant laboratory results or abnormal results during the study period will be presented in shift tables.

For the laboratory measurements, shift tables will be presented in terms of Low (L), Normal (N), High (H), Missing (M). High and Low measurements will be based on reference ranges provided by the laboratory at the study site.

Clinical laboratory results will also be presented in data listings.

10.6.1.3 Anti-rhHNS Antibody Formation

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by assay methodology used to identify antibodies, number and percentage of positive and negative specimens by evaluation visit and/or study week, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status. These results will also be presented in data listings.

10.6.2 Secondary Analysis

10.6.2.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of rhHNS administration on QoL measures will be examined by presenting mean change from baseline across dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.2.2 Pharmacodynamic Analyses

To determine the effects of rhHNS administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparin sulfate reduction (in CSF and urine) will be examined using mean change and the corresponding 95% confidence interval. The concentration of inflammatory cytokines in serum and CSF will also be examined. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

The planned analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. On-site review of the eCRF's for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

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

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

Before Shire HGT initiates the trial (ie, obtains informed consent [assent if applicable] from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available to Shire HGT or their designee:

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire HGT. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire HGT.

11.8 Data Monitoring Committee

There will be no data monitoring committee for this study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire HGT and the Investigators. In addition, a decision on the part of Shire HGT to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.8.3).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

12 LIST OF REFERENCES

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Appendix 1 Schedule of Events

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of rhHNS Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[i] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[h]**
Informed Consent/Enrollment		●				
Physical Examination	●	●	●		●	
Height and Weight	●	●			●	
Head Circumference	●			●	●	
Visual and Hearing Assessment				●	●	
ECG	●		●[b]		●	
Vital Signs	●	●	●		●	
Hematology	●	●			●	
Serum Chemistry	●	●			●	
Pregnancy Testing[l]	●	●				
Urinalysis	●	●			●	
Leukocyte pellet preparation[m]	●					
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Plasma and serum Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[j]	●			●	●	
Auditory Brainstem Response (ABR)	●			●	●	
MRI of the Head	●			●	●	
CSF Sample Collection[k]	●		●[c]		●[c]	
rhHNS dosing: every 28 (±7) days[g]			●			
Neurological Examination	●	●	●		●	
Full Neurodevelopmental Testing	●			●	●	
Children's Sleep Habits Rating Scale	●			●	●	
Child Health Questionnaire-50	●			●	●	
Child Health Questionnaire-87	●			●	●	

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of rhHNS Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[i] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[h]**
Infant Toddler QOL Questionnaire	●			●	●	
Concomitant Medications, Therapies, and Procedures	●	●	●		●	●
Adverse Event Monitoring	●	●	●		●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; ECG = electrocardiogram; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as presented here at Month 54, corresponds to Month 48 in HGT-SAN-067, but represents a total of 54 months of study treatment (48 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] CSF samples will be obtained according to the process with in the study operations manual). An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of rhHNS and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or a LP may be performed (can occur up to 5 times in a 6 month period).

[d] Patients may be discharged as early as 8 hours post rhHNS infusion (ie, on Day 2)when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[i] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled rhHNS IT dose.

[j] Blood sample drawn before IT injection of rhHNS.

[k] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

[l] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[m] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

Appendix 2 Neurodevelopmental and Behavioral Assessments

Table 4-1 and Table 4-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table 4-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table 4-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child's abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III)[23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]

Purpose:

The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS) [5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Failure of IDDD Function: Investigation and Management

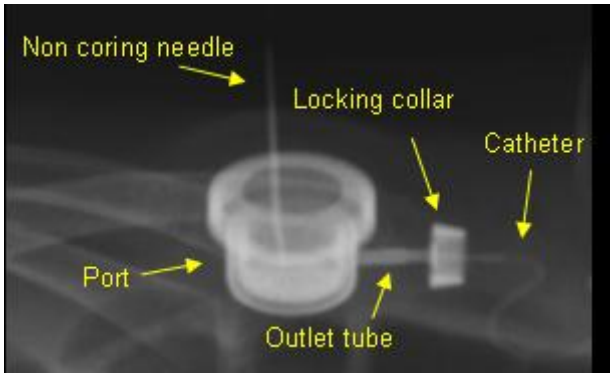
This appendix is intended to assist in the investigation of mechanical device failure and its subsequent management.

Note: The total number of IDDD revisions a patient may undergo will be limited to 2 (partial or complete replacements) in a 6 month period (including the time in HGT-SAN-055). Additionally, the total number of X-rays to investigate and verify IDDD integrity will be limited to 6, in a 6-month period plus up to 3 intra-operative fluoroscopies to guide catheter placement.

Introduction

The device consists of a catheter, inserted into the intrathecal space in the lower lumbar area, tunneled subcutaneously to a site overlying an ipsilateral (so the tunneled catheter does not cross the midline) lower rib in the mid to anterior axillary line, and there connected to the subcutaneous port. The catheter is connected to the metal outlet tube from the port via a plastic collar, secured by a metal locking ring. The port is accessed percutaneously for CSF aspiration and drug administration, via a special non-coring needle. The metal chamber within the port, the locking ring, and the catheter are radio-opaque (Figure 1). An X-ray taken post-implantation is used to verify and document 1) the correct location of the catheter tip in the mid-thoracic spinal canal, and 2) the correct orientation and position of the metal locking ring that secures the catheter to the port outlet tube.

Figure 1: Radiographic appearance of IDDD port implanted over lower ribs, with percutaneous needle inserted. Note that the tapered appearance of the locking collar permits assessment of its correct orientation.



Functional failure of the IDDD is most likely to be mechanical: blockage may occur as a result of luminal occlusion, fibrin sheath formation around the tip, external compression or kinking. Leakage may be a consequence of catheter disconnection or fracture, or breakage of the port outlet tube itself. In addition, the catheter may become dislodged from the spinal canal (see Smith's Medical instructions [provided in the Investigator Brochure] for additional details).

Details of the surgical implantation procedure, designed to minimize the chance of these problems arising, are contained in the Smith's Medical Instructions for Use and Shire Study Training materials.

In addition, medical complications may also preclude use of the IDDD, and may lead to its removal, revision, or replacement. These include infection, hematoma, inadvertent epidural placement, pain on injection, etc, as listed in the Smith's Medical Instructions for Use. These complications should be managed as clinically indicated.

Investigation

Diagnostic clues of mechanical failure, established or impending include:

- Increasing difficulty in aspirating CSF from the IDDD
- Blood stained appearance of CSF
- Increasing difficulty in pushing drug or sterile normal saline through the IDDD
- Soft tissue swelling indicating possible fluid accumulation at the site of the port, or along the course of the catheter, immediately following administration of drug and/or saline via IDDD
- Increased cellularity of the pre-treatment CSF sample

Note: increased cellularity of the CSF may also indicate meningeal reactions to the drug or the presence of infection, and so must be interpreted in the context of the whole clinical picture.

Approach to investigation:

1. Clinical evaluation for swelling following drug infusion
2. X-ray imaging, to include both the port and the full length of the catheter in the spinal canal. X-rays are probably the single most useful investigational approach. Especially when compared with post-implantation confirmatory images, this may elucidate:
   A. Slippage of the catheter from the spinal canal
   B. Breakage or disconnection of the catheter and/or its locking device from the port assembly
   C. Kinking of the catheter

Note: There is no information on compatibility of the IDDD and drug product with contrast media, so these should be avoided.

Management:

1. In general, once mechanical failure of the IDDD has occurred, intervention should be planned to replace the IDDD in part or in its entirety.
2. CSF may be aspirated, and drug administered via lumbar puncture while awaiting IDDD revision, in accordance with the protocol.
3. If IDDD mechanical failure is confined to the port, its attachment to the catheter, or to the segment of catheter immediately adjacent to the port, proximal revision of the IDDD may be undertaken. In such an event, the old port and locking assembly is removed. New components are then implanted, leaving the original catheter in situ. However, the end of the catheter must be trimmed by at least one centimeter to restore a tight connection with the new port outlet tube. The patency of the apparatus must be ascertained intra-operatively, by aspirating CSF through the port, and flushing the device with sterile normal saline.

4. If IDDD mechanical failure is due to dislodgment of the catheter from the spinal canal, kinking at a location distal to the immediate vicinity of the port, or unresolved by proximal revision, the whole device must be replaced, following the instructions provided by Smith's Medical and the Shire training materials.

Note: All removed IDDDs must be returned to Smith's Medical for further analysis. Please refer to the Study Manual for instructions on the IDDD Return process. You should also contact Shire HGT.

Note: All IDDD related AEs (serious and nonserious) will be reported to Shire; all IDDD related SAEs will also be reported to Global Shire PVRM.

Drug Administration Following Device Revision:

1. If a full revision of the IDDD has been performed, an interval of 7 days is required before resuming administration of drug via IDDD.
2. If a proximal (ie, replacement of port only) revision of IDDD has been performed, drug administration through the IDDD can proceed immediately post-operatively.
3. In the event that the IDDD fails after 2 revisions in a 6-month time period, rhHNS may be administered and CSF collected by lumbar puncture for up to 5 successive months after which, IDDD re-implantation or revision must occur.

Appendix 4 Summary of Changes for Amendment 2

Clinical protocol HGT-SAN-067 has been revised from the previous version (amendment 1, 27-Jan-2011) to change the dose and regimen administered to patients in Group 3, the dose was changed from 45 mg Q2W to 90 mg every month (Q4W). This change was made to ensure consistency with the revised HGT-SAN-055 study protocol and will allow patients to continue to receive the same dose in this extension study as they did in the original study. Other changes made to this amendment include: The addition of an appendix detailing the identification and management of non-functioning IDDDs. The number of permissible IDDD revisions and X-rays was specified and is aligned with similar changes made to HGT-SAN-055. Study stopping rules have been added. A number of study procedures have been aligned with changes made to HGT-SAN-055. In addition, the Sponsor's address and Medical Monitor's contact details were changed.

The changes relative to amendment 1 of the protocol (27-Jan-2011) are summarized below by section number; new or additional text is indicated in bold and deleted text is indicated as strikethrough. Other sections affected by the same change are listed below each change.

Please note that only changes of substance are displayed here.

Change: The text was modified state the revise dose and regimen for patients in Group 3.
Section impacted by this change: Section 6.2 Treatment Administered
Modified Text: rhHNS for IT administration will be provided by Shire HGT. rhHNS will be administered by an IDDD. Following the review and signing of informed consent, eligible patients will receive the same dose of rhHNS they received in Study HGT-SAN-055: • Group 1: rhHNS administered by IT injection 10 mg once per month **(Q4W)** • Group 2: rhHNS administered by IT injection 45 mg once per month **(Q4W)** • Group 3: rhHNS administered by IT injection ~~45 mg Q2W~~ **90 mg once per month (Q4W)**
Other sections affected by the same change: Synopsis, Introduction, Section 4.1, Section 5.2, Section 6.2.1, and Appendix 1 Schedule of Events.

Change: Text was added to clarify the administration of study drug via lumbar puncture in the event of a non-functional IDDD
Section impacted by this change: Section 6.2.4 Administration of rhHNS via Lumbar Puncture
In the event of a non functional IDDD, rhHNS may be administered by lumbar puncture (LP), for re implantation of a new IDDD (see Section 7.11) up to 5 successive months. The performance of LP is at the discretion of the Investigator.

If a lumbar puncture is to be performed, the patient is likely to require general anesthesia with appropriate airway management. Once the patient is anesthetized, a lumbar puncture will be performed and a CSF sample will be obtained. Some cases may be managed with conscious sedation, if this is considered by the investigator to be adequate for the safe and expeditious performance of a LP.
Other sections affected by the same change: Synopsis, Section 6.2.3

Change: The number of permissible IDDD revisions and X-rays was specified and is aligned with similar changes made to HGT-SAN-055.
Section impacted by this change: Section 7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD
Modified Text: This section was added to the protocol **A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in 6-month period, also including the time in HGT-SAN-055.**
Other sections affected by the same change: Synopsis, Section 6.2.3

Change: Genistein was specified in the Concomitant Therapy and the Drug dictionary used was corrected
Section impacted by this change: Section 6.5 Concomitant Therapy
Modified Text: All non-protocol treatments and procedures that occur from the time of informed consent (**and** assent, if applicable) through the safety follow-up contact are regarded as concomitant and will be documented on the appropriate pages of the electronic case report form (eCRF). Concomitant therapy includes medications **(including Genistein),** therapies/interventions administered to patients, and medical/surgical procedures performed on the patients. Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 **WHO** Drug **Dictionary (WHO-DD)** ~~Drug Reference List (WHODRL~~**).**
No other sections were affected by these changes

Change: Text was added to clarify that MRIs will be centrally read.
Section impacted by this change: Section 7.11 MRI of the Head
Modified Text: The regional brain volume will be assessed through an MRI of the head. The patient will be under general anesthesia for this assessment. ~~The central reading for MRI data, across all sites~~ **All MRIs** will be ~~completed at~~ **centrally read by** the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.
No other sections were affected by this change

Change: Clarifications were made to the Inclusion and Exclusion Criteria, and 1 exclusion criterion was deleted as it was covered by the inclusion criterion requiring signed informed consent for the study.
Section impacted by this change: Section 5.2 Inclusion Criteria and 5.3 Exclusion Criteria
Modified Text: 1. ~~Patients~~ **The patient** must have completed ~~all study requirements~~ **Study HGT-SAN-055** and ~~assessments for Study HGT-SAN-055 prior to enrolling~~, in ~~this extension study and must have~~ **the opinion of the investigator, has** no safety or medical issues that contraindicate participation. 2. The patient, patient's parent(s) or legally authorized ~~guardian~~ **representative**(s) ~~**must have**~~ **has** voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent **(and assent, if applicable)** form after all relevant aspects of the study have been explained and discussed with the patient, **the** ~~guardians~~**'patient's, patient's parents or legally authorized representative's** consent and patient's assent as ~~**relevant**~~ **appropriate**, must be obtained **prior to any study specific procedures**. 3. The patient has received ~~and tolerated treatment with~~ **at least 5 of the 6 planned infusions of** rhHNS, ~~completed the End of Study visit, and has received at least 80% of the total planned infusions within the last 6 months in study~~ **in the** HGT-SAN-055 ~~(ie, at least 5/6 ([Group 1 or 2] or 10/12 infusions [Group 3]) study~~. **Exclusion:** 10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA ~~or used any other intrathecal delivery device other than what was used in Study HGT-SAN-055,~~ within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact). ~~12 The patient's parent(s), or patient's legal guardian(s) is/are unable to provide consent or the patient cannot provide assent, as appropriate, due to, but not limited to, the inability~~

~~to understand the nature, scope, and possible consequences of the study, or do/does not agree to comply with the protocol defined schedule of assessments.~~
Other sections affected by the same change: Synopsis

Change: Text was added to state the study's stopping rules
Section impacted by this change: Section 7.23 Safety-related Study Stopping Rules
Modified Text: This section was added to the protocol **If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered possibly, probably, or definitely related to study drug, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered possibly, probably, or definitely related to the study drug by the sponsor, then the site will be instructed to halt further rhHNS administration to all patients and the safety data reviewed (see Section 7.23). Following that review of safety data, the study will be either:** • **Resumed unchanged** • **Resumed with modifications to the protocol or** • **Terminated** **Patient safety will be monitored on a continuous basis during this study until the last patient completes his or her last scheduled study visit/assessment**
Other sections affected by the same change: none

Change: Text was added to state that there will be no protocol exemptions to this study
Section impacted by this change: Section 11.9 Protocol Violations/Deviations
Modified Text: the following sentence was added to the protocol **There will be no protocol exemptions granted for this study.**
Other sections affected by the same change: none

Change: Text was added to document the potential adverse events in response to IT rhHNS
Section impacted by this change: Section 7.22.2.1 Adverse Events
Modified Text: This section was added to the protocol **POTENTIAL ADVERSE EVENTS: INTRATHECAL RECOMBINANT HUMAN HEPARAN N-SULFATASE** **Adverse Events Due to Systemic Exposure to rhHNS** **Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion related reactions. An infusion related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.**
Other sections affected by the same change: none

Change: Text was added to clarify the end of study procedures for patients that withdraw early
Section impacted by this change: Section 8.3 End of Study/Early Termination Procedures: Month 55
Modified Text: the following text was added to the protocol **Patients who discontinue early: All patients who discontinue early will have their IDDD removed.** **Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.** **Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments**
Other sections affected by the same change: none

Change: It was clarified that the nomenclature of the study months began with the time in the HGT-SAN-055 study
Sections impacted by this change: Appendix 1 Schedule of Events
Added Text: **(from the start of HGT SAN 055)**
Other sections affected by the same change: Synopsis, Section 4, Section 7, and Section 8.

Change: The length of time a patient has to remain in the study unit after receiving study drug was reduced from 24 hours to 8 hours.
Sections impacted by this change: Synopsis
Modified Text: Patients will remain in the study centre for at least ~~24~~ **8** hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.
Other sections affected by the same change: Section 4.1, Section 6.2.1, and Section 6.2.3.

Change: Text stating compliance with the Declaration of Helsinki has been removed.
Sections impacted by this change: Section 11.3 Ethical Conduct of the Study
Deleted Text: ~~Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.~~
No other sections are affected by this change.

Change: A number of study procedures were changed to align with the procedures performed in HGT-SAN-055
Sections impacted by this change: Section 7.
The following parameters were either added to the protocol or their frequency of assessment was changed • **Plasma and** serum heparan sulfate and heparan sulfate derivatives • The frequency of pregnancy testing was increased • **Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material**
Other sections affected by these changes: Appendix 1 Schedule of Events

Change: Additional of New Appendix
Sections impacted by this change: Appendix 4
The following titled appendix was added to the protocol: **•Appendix 3 Failure of IDDD Function: Investigation and Management**
Other sections affected by the same change: none

Appendix 5 Protocol Signature Page

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 Amendment 2
Final Date:	21 June 2010
Amendment 1 Date:	22 January 2011
Amendment 2 Date:	13 January 2012

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

Signatory:

Investigator

Signature **Date**

<enter text>

Printed Name

I have read and approve the protocol described above.

Signatory:

Shire HGT Medical Monitor

Signature **Date**

[redacted] MD

Printed Name

Appendix 6 The National Cancer Institute Common Toxicity Criteria

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421, United States
Medical Monitor:	[redacted] MD, [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012
Amendment 3:	28 August 2012

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421, United States

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS)

Name of Active Ingredient:

rhHNS

Name of Inactive Ingredient:

N/A

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

Study Phase: I/II

Study Objectives:

Primary Objective:

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received rhHNS via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy in study HGT-SAN-067.

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

The primary endpoint of this study is:

- To determine the long-term safety of intrathecal rhHNS administration, as measured by the adverse events (type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), electrocardiograms (ECG), cerebrospinal fluid (CSF), chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of rhHNS in CSF and serum.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and/or CSF, and if possible, in serum and/or plasma.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of rhHNS via an IDDD in patients with 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 rhHNS treatment. Patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of rhHNS in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first rhHNS dose in HGT-SAN-067.

Enrolled patients will check in to the study center 1 day before each of the scheduled rhHNS dosing days for safety assessments (designated Day 1). If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least 8 hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out. A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study). Note: X-rays may be performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy may be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055).

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria will be applied and will be based on the types and severity of adverse events (AEs) reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of rhHNS (ie, Month 55). The EOS procedures will include 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, and MRI.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of rhHNS. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the protocol appendix which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of rhHNS, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), rhHNS will be administered via lumbar puncture (LP). Study drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with rhHNS.

Test Product; Dose; and Mode of Administration:

Recombinant human heparan N-sulfatase (rhHNS) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly).

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.

2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of rhHNS in the HGT-SAN-055 study.
4. The Patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Subjects will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.
3. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

Duration of Treatment:

The study duration will be 4 years.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods:

The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval around the mean will be presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 3: 28 August 2012

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CNS	central nervous system
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CO_2	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
CRIM	cross-reacting immunologic material
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other hweek

FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
H	High
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonization
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
L	Low
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M	Missing
M6P	mannose-6-phosphate
MABC-2	Movement Assessment Battery for Children
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
MABC-2	Movement Assessment Battery for Children, Second Edition
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
N	Normal
Na	sodium
PE	pressure-equalization
QoL	quality of life
Q4W	once per month
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)
WHO-DD	WHO Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. The patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is a lysosomal storage disease (LSD) caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A (MPS IIIA) results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtypes A and B similar in prevalence, accounting for approximately 90% of all cases of MPS III.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1-,3] In summary, MPSIIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5 - 7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8]

A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11, 12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the rhHNS clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an intrathecal drug delivery device (IDDD) due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13, 14 -,16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L-Idurunonidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358).

This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse events monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire HGT-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of rhHNS in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, rhHNS was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of rhHNS leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of rhHNS to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 µg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 µg dose given IT every-other-week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mg rhHNS given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, the highest dose of rhHNS was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no rhHNS-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene.

In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs, rhHNS (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of rhHNS into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg rhHNS resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis, astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg rhHNS per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of rhHNS (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg rhHNS was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 Study Rationale

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

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the end of study (EOS) evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will continue to receive rhHNS at the same dose and schedule as they received in Study HGT-SAN-055. The dose for each group will remain unchanged during this study unless safety and/or efficacy analyses of HGT-SAN-055 data indicate otherwise. Meaningful composite analysis of the optimum dose and regimen will come only after all 3 dose groups complete the entire HGT-SAN-055 study.

Please refer to the current edition of the rhHNS Investigator's Brochure for further information.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

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

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

To determine the long-term safety of IT rhHNS administration, as measured by adverse events (by type and severity), changes in clinical laboratory testing (serum chemistry including liver function tests, hematology, and urinalysis), ECG, CSF, chemistries (including cell counts and inflammatory markers), and anti-rhHNS antibodies (in CSF and serum).

3.2 Secondary Endpoints

The secondary endpoints of this study are 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 rhHNS in CSF and serum.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine, plasma, and serum.
- Brain MRI and ABR, (also know as Brainstem Auditory Evoked Potentials).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of IT administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of rhHNS via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted rhHNS treatment. Patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

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

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 patient received their first IT dose of rhHNS in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first rhHNS dose in HGT-SAN-067.

Enrolled patients will check in to the study center 1 day before each of the scheduled rhHNS dosing days for safety assessments (designated Day 1). If no safety concerns exist, the patient will subsequently receive IT administration of rhHNS on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least 8 hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out.

A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055).

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 electronic case report forms (eCRFs). Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of rhHNS (ie, Month 55). The EOS procedures will include 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, and MRI. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of rhHNS. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to protocol Appendix 3 which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. A maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of rhHNS, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, rhHNS will be administered via LP. Drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of rhHNS via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT rhHNS administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with rhHNS in the HGT-SAN-067 study.

4.3 Study Duration and Dates

The study duration will be 4 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue rhHNS treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of rhHNS in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with rhHNS.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in rhHNS drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than rhHNS) intended as a treatment for MPS IIIA within the 30 days prior to, or during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

rhHNS for IT administration will be provided by Shire HGT. rhHNS will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will receive the same dose of rhHNS they received in Study HGT-SAN-055:

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

6.2.1 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT rhHNS dosing for safety assessments, designated Day 1, on each rhHNS treatment week, and if no safety concerns exist, will receive IT administration of rhHNS on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the Investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least 8 hours following dosing with rhHNS and will be discharged from the unit when deemed clinically stable by the Investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details). In the event of a non-functional IDDD, rhHNS may be administered by LP, for up to 5 successive months (see Section 6.2.4).

6.2.2 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for safety evaluation and biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the Study Operations Manual. CSF opening pressure will be measured whenever a LP is performed, and at the time of IDDD revision (partial or replacement). Additional CSF samples may be taken during this time.

6.2.3 Intrathecal Administration of rhHNS

rhHNS will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive rhHNS via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 8 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.2.4). The investigation and management of a malfunctioning IDDD is detailed in Appendix 3. If the failure is mechanical, partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.2.4 Administration of rhHNS via Lumbar Puncture

In the event of a non functional IDDD, rhHNS may be administered by LP, for up to 5 successive months. The performance of a LP is at the discretion of the Investigator.

If a LP is to be performed, the patient may require general anesthesia with appropriate airway management. Once the patient is anesthetized, a LP will be performed and a CSF sample will be obtained. Some cases may be managed with conscious sedation, if this is considered by the investigator to be adequate for the safe and expeditious performance of a LP.

6.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with rhHNS. Patients will remain in the groups (1, 2, or 3) they were assigned to in Study HGT-SAN-055.

6.4 Blinding

Not applicable; as this trial is not blinded.

6.5 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 WHO Drug Dictionary (WHO-DD).

6.6 Restrictions

6.6.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than rhHNS or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.6.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.6.3 Patient Activity Restrictions

There are no restrictions on patient activity in this study.

6.7 Treatment Compliance

rhHNS is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.8 Packaging and Labeling

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of rhHNS. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminum seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9 Storage and Accountability

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

6.10 Investigational Product Retention at Study Site

All rhHNS study drug delivered to an Investigator will be recorded and accounted for throughout the study. All rhHNS study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory and/or Study Operations Manual.

7.2 Physical Examination

A physical examination of each patient will be performed as detailed in Appendix 1 Schedule of Events.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.10). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory and/or Study Operations Manual.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.8 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.8.1.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.8.1.2 Urine Heparan Sulfate and Heparan Sulfate Derivatives

A urine sample will be collected for the determination of heparan sulfate and heparan sulfate derivatives and the analysis will be performed at Shire HGT or designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.8.2 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.8.2.1, 7.8.2.2, and 7.8.2.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or RNA may become used as they become available in the future.

7.8.2.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.8.2.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire HGT laboratories.

7.8.2.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of anti-rhHNS antibodies at Shire HGT or Shire HGT designated laboratories.

7.8.2.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of MPS exploratory biomarkers at Shire HGT laboratories.

7.8.3 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual to be provided by Shire HGT.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.9 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.10 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.11 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. Management details are provided in Appendix 3. Procedures for implantation are detailed in the device's Instructions for Use Manual and in the training materials provided by Shire HGT. The patient will be under general anesthesia for this procedure. The CSF opening pressure will be recorded when the intrathecal space is first entered at the time of the IDDD re-implantation. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly (correct orientation of the locking device on the access port), and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the Study Operations Manual).

A post-operative check of the IDDD and incision will be performed on Day 4 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision or replacement is done.

7.14 Dispensing Study Drug

rhHNS will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. rhHNS will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, rhHNS may be administered via LP. See Section 6.2.4 for details.

7.15 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.16 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

7.17 Anti-rhHNS Antibody, Heparan Sulfate, and Heparan Sulfate Derivative Determination

Blood samples will be collected and evaluated at Shire HGT laboratories for the determination of anti-rhHNS antibodies, and plasma and serum heparan sulfate and heparan sulfate derivatives. Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual.

7.18 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.19 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.20 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.20.1, 7.20.2, and 7.20.3.

7.20.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age

7.20.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being

7.20.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.21 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.22 Adverse Events

7.22.1 Definitions of Adverse Events and Serious Adverse Events

7.22.1.1 Adverse Event

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

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

Throughout the study, the Investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to study drug. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All adverse events should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of rhHNS. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to rhHNS caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of rhHNS to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs.

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal rhHNS therapy to date.

POTENTIAL ADVERSE EVENTS: INTRATHECAL RECOMBINANT HUMAN HEPARAN N-SULFATASE

Adverse Events Due to Systemic Exposure to rhHNS

Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

Adverse Events Related to the Direct Delivery of rhHNS to the CNS through Intrathecal Administration

Examples of adverse events observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory parathesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time.

POTENTIAL ADVERSE EVENTS: IDDD-RELATED ADVERSE EVENTS

Examples of adverse events related to the insertion or use of an IDDD include, but are not limited to, the following: catheter disconnection or fracture, erosion of portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, malposition of catheter, migration of portal/catheter, occlusion of portal/catheter, portal site or subcutaneous tract infection, and sepsis.

In addition, there are risks associated with intraspinal access, which include the following: cerebrospinal fluid leaks, dura mater or epidural vein perforation, epidural or intrathecal space infection (which could result in meningitis), inadvertent epidural placement, pain on injection, and spinal cord or nerve injury.

7.22.1.2 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3.

The severity of all AEs/SAEs should be recorded on the appropriate eCRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3 Adverse Event Severity

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

Relationship of an adverse event or serious adverse event to study medication is to be determined by the Investigator based on the definitions in Table 7-4:

Table 7-4 Adverse Event Relatedness

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

7.22.2 Procedures for Recording and Reporting Adverse Events

7.22.2.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire HGT Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study procedure. The Investigator will promptly supply all information identified and requested by the Sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device or procedure.

The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted] United Kingdom OR
United States FAX: [redacted]
Email: [redacted]
AND
Shire HGT Medical Monitor:
FAX: [redacted] (United States)

The Investigator may also call the Medical Monitor directly (optional):

Shire HGT Medical Monitor: [redacted], MD
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted] (24 hour access)
Email: [redacted]
AND
Clinical Project Manager CC'd: [redacted]

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

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

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

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication

7.22.2.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, “How do you feel?”) and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient’s parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider’s observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. In addition, the relationship of each AE to study medication must be recorded.

7.22.2.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient’s participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The Investigator should inform the patient, the patient’s parent(s), or the patient’s legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire HGT Medical Monitor (see Section 7.22.2.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The Investigator or other physician in attendance in such an emergency must contact the Shire HGT Medical Monitor as soon as possible.

The Investigator, along with the Shire HGT Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.23 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered possibly, probably, or definitely related to study drug, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered possibly, probably, or definitely related to the study drug by the sponsor, then the site will be instructed to halt further rhHNS administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.24 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of rhHNS throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of rhHNS. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a pregnancy test is positive the patient will be discontinued from the study, and the Investigator must contact the Shire HGT Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.25 Removal of Subjects from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.26 Other Study Procedures

This section is not applicable.

7.27 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first rhHNS dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last rhHNS administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of rhHNS in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal rhHNS dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
  - Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
  - ABR
  - MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments performed prior to the administration of anesthesia)
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments

Patients will receive rhHNS IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection. Note: Patients will not receive study drug if the pre-dose CSF contains >100 WBC per cubic millimeter.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs
- Hematology
- Serum chemistry
- Urinalysis
- Pregnancy testing (applicable females only)
- Neurological examination (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal rhHNS treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, AND 54

- Head circumference
- Visual and hearing assessments
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and /or serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR
- MRI of the head
- Full neurodevelopmental testing, including VABS-II (performed prior to the administration of anesthesia and the rhHNS IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of rhHNS

Patients may be discharged from the clinical site 8 hours after dosing, if deemed stable by the Investigator.

- Physical examination
- ECG (performed following IT study drug injection)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- rhHNS IT injection (Day 2 ±2 days)
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

8.3 End of Study/Early Termination Procedures: Month 55

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of rhHNS.

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Scheduled removal of the IDDD will be required at study completion with sedation or anesthesia, as required.

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR
- MRI of the head
- CSF sample collection
- Neurological examination
- Full neurodevelopmental testing, including VABS-II
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

All patients who discontinue the study early will have their IDDD removed.

Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 56

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures

- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire HGT or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of rhHNS in patients with MPS IIIA. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time.

All hypothesis tests will be 2-sided and will be performed at the 0.05 level. Hypothesis testing will be viewed as exploratory. Any resulting p-values will not be regarded as a firm support for conclusions, but rather suggestive of areas of examination in future studies. In general, variables will be quantified as a change from the baseline value. The null hypothesis will be that there is no difference in the change from baseline between dose groups. Note that the baseline visit for this study will be the first day the patient received his/her IT dose of rhHNS in study HGT-SAN-055.

The primary objective of this trial is to assess the long term safety of rhHNS administration via a surgically implanted IDDD. Hence an extensive safety assessment will be performed. The safety analyses will consist of all enrolled patients. To evaluate safety, adverse experiences will be tabulated by dose group. Vital signs, electrocardiograms, serum and CSF components and chemistries, hematology, and urinalysis safety monitoring will be listed for each patient and abnormal values will be flagged. In addition, anti-rhHNS antibodies (in CSF and serum) will also be listed. No formal statistical tests will be performed on the safety parameters.

10.2 Determination of Sample Size

Since this is an extension study, sample size is determined by the number of patients who completed HGT-SAN-055 (maximum of 12 patients) and elected to continue treatment with rhHNS in this study

10.3 Analysis Populations

The analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. Both safety and efficacy analyses would be performed using the above mentioned population.

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew, by dose group. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of adverse events, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients will be included in the safety analysis. Patients will be grouped according to the actual dose received.

No formal statistical test will be performed in the safety evaluations. Vital sign measurements, clinical chemistry, and hematology safety monitoring will be listed for each patient, and abnormal values will be flagged. These will also be summarized at each time point, including change from baseline.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in system organ class, and having each individual adverse event. Note that in any given category (eg, system organ class) a patient will only be counted once. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication.

Adverse events that occur up to 30 days after the last dose of study drug will be considered "on-treatment". Adverse events which are deemed probably, possibly, or definitely related to the device will be summarized by dose group and overall.

Laboratory data will be listed by patient and dose group. Patients with newly occurring abnormalities outside the normal range will be flagged and listed separately and summarized. Mean change from baseline values or shift tables will also be provided by dose group at each visit.

Vital signs data will be listed by patient and dose group. Furthermore, mean changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

Electrocardiograph assessments will be listed by patient and dose group. Mean changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.1.2 Clinical Laboratory Evaluations

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis) results will be presented in summary tables by evaluation visit using number of patients (n), mean, median, standard deviation, minimum, and maximum. Changes from baseline will be summarized for each post-baseline visit. The number of patients with clinically significant laboratory results or abnormal results during the study period will be presented in shift tables.

For the laboratory measurements, shift tables will be presented in terms of Low (L), Normal (N), High (H), Missing (M). High and Low measurements will be based on reference ranges provided by the laboratory at the study site.

Clinical laboratory results will also be presented in data listings.

10.6.1.3 Anti-rhHNS Antibody Formation

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by assay methodology used to identify antibodies, number and percentage of positive and negative specimens by evaluation visit and/or study week, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status. These results will also be presented in data listings.

10.6.2 Secondary Analysis

10.6.2.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of rhHNS administration on QoL measures will be examined by presenting mean change from baseline across dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.2.2 Pharmacodynamic Analyses

To determine the effects of rhHNS administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparin sulfate reduction (in CSF and urine) will be examined using mean change and the corresponding 95% confidence interval. The concentration of inflammatory cytokines in serum and CSF will also be examined. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

The planned analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

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

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

Before Shire HGT initiates the trial (ie, obtains informed consent [assent if applicable] from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available to Shire HGT or their designee:

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire HGT. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire HGT.

11.8 Data Monitoring Committee

There will be no data monitoring committee for this study.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire HGT and the Investigators. In addition, a decision on the part of Shire HGT to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.8.3).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

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Appendix 1 Schedule of Events

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of rhHNS Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)	EOS[f] Month 55 (from the start of HGT-SAN-055)	Month 56 Safety Follow-up[j]
Informed Consent/Enrollment		●				
Physical Examination	●	●	●		●	
Height and Weight	●	●			●	
Head Circumference	●			●	●	
Visual and Hearing Assessment				●	●	
ECG	●		●[b]		●	
Vital Signs	●	●	●		●	
Hematology	●	●			●	
Serum Chemistry	●	●			●	
Pregnancy Testing[n]	●	●				
Urinalysis	●	●			●	
Leukocyte pellet preparation[o]	●					
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Plasma and serum Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[l]	●			●	●	
Auditory Brainstem Response (ABR)	●			●	●	
MRI of the Head	●			●	●	
CSF Sample Collection[m]	●		●[c]		●[c]	
rhHNS dosing: every 28 (±7) days [g, d]			●			
Neurological Examination[h]	●	●	●		●	
Full Neurodevelopmental Testing[i]	●			●	●	
Children's Sleep Habits Rating Scale	●			●	●	
Child Health Questionnaire-50	●			●	●	
Child Health Questionnaire-87	●			●	●	
Infant Toddler QOL Questionnaire	●			●	●	

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of rhHNS Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**
Concomitant Medications, Therapies, and Procedures	●	●	●		●	●
Adverse Event Monitoring	●	●	●		●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; EOS = end of study ; ECG = electrocardiogram; IT = intrathecal; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as presented here at Month 54, corresponds to Month 48 in HGT-SAN-067, but represents a total of 54 months of study treatment (48 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] CSF samples will be obtained according to the process with in the study operations manual). An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of rhHNS and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or a LP may be performed (can occur up to 5 times in a 6 month period).

[d] Patients may be discharged as early as 8 hours post rhHNS infusion (ie, on Day 2) when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] The neurological exam should not occur sooner than 4 hours after administration of study drug or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

[i] Full neurodevelopmental testing includes an assessment with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

[j] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[k] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled rhHNS IT dose.

[l] Blood sample drawn before IT injection of rhHNS.

[m] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

[n] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[o] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

Appendix 2 Neurodevelopmental and Behavioral Assessments

Table 4-1 and Table 4-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table 4-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table 4-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child's abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III) [23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II) [24]

Purpose:

The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS) [5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Failure of IDDD Function: Investigation and Management

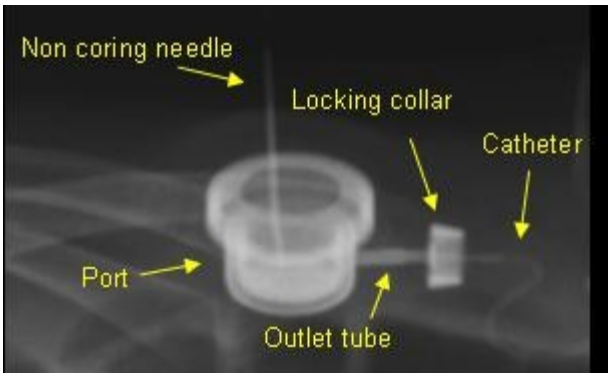
This appendix is intended to assist in the investigation of mechanical device failure and its subsequent management.

Note: The total number of IDDD revisions a patient may undergo will be limited to 2 (partial or complete replacements) in a 6 month period (including the time in HGT-SAN-055). Additionally, the total number of X-rays to investigate and verify IDDD integrity will be limited to 6, in a 6-month period plus up to 3 intra-operative fluoroscopies to guide catheter placement.

Introduction

1. The device consists of a catheter, inserted into the intrathecal space in the lower lumbar area, tunneled subcutaneously to a site overlying an ipsilateral (so the tunneled catheter does not cross the midline) lower rib in the mid to anterior axillary line, and there connected to the subcutaneous port. The catheter is connected to the metal outlet tube from the port via a plastic collar, secured by a metal locking ring. The port is accessed percutaneously for CSF aspiration and drug administration, via a special non-coring needle. The metal chamber within the port, the locking ring, and the catheter are radio-opaque (Figure 1). An X-ray taken post-implantation is used to verify and document 1) the correct location of the catheter tip in the mid-thoracic spinal canal, and 2) the correct orientation and position of the metal locking ring that secures the catheter to the port outlet tube.

Figure 1: Radiographic appearance of IDDD port implanted over lower ribs, with percutaneous needle inserted. Note that the tapered appearance of the locking collar permits assessment of its correct orientation.



Functional failure of the IDDD is most likely to be mechanical: blockage may occur as a result of luminal occlusion, fibrin sheath formation around the tip, external compression or kinking. Leakage may be a consequence of catheter disconnection or fracture, or breakage of the port outlet tube itself. In addition, the catheter may become dislodged from the spinal canal (see Smith's Medical instructions [provided in the Investigator Brochure] for additional details).

Details of the surgical implantation procedure, designed to minimize the chance of these problems arising, are contained in the Smith's Medical Instructions for Use and Shire Study Training materials.

In addition, medical complications may also preclude use of the IDDD, and may lead to its removal, revision, or replacement. These include infection, hematoma, inadvertent epidural placement, pain on injection, etc, as listed in the Smith's Medical Instructions for Use. These complications should be managed as clinically indicated.

Investigation

Diagnostic clues of mechanical failure, established or impending include:

- Increasing difficulty in aspirating CSF from the IDDD
- Blood stained appearance of CSF
- Increasing difficulty in pushing drug or sterile normal saline through the IDDD
- Soft tissue swelling indicating possible fluid accumulation at the site of the port, or along the course of the catheter, immediately following administration of drug and/or saline via IDDD
- Increased cellularity of the pre-treatment CSF sample

Note: increased cellularity of the CSF may also indicate meningeal reactions to the drug or the presence of infection, and so must be interpreted in the context of the whole clinical picture.

Approach to investigation:

1. Clinical evaluation for swelling following drug infusion
2. X-ray imaging, to include both the port and the full length of the catheter in the spinal canal. X-rays are probably the single most useful investigational approach. Especially when compared with post-implantation confirmatory images, this may elucidate:
   A. Slippage of the catheter from the spinal canal
   B. Breakage or disconnection of the catheter and/or its locking device from the port assembly
   C. Kinking of the catheter

Note: There is no information on compatibility of the IDDD and drug product with contrast media, so these should be avoided.

Management:

1. In general, once mechanical failure of the IDDD has occurred, intervention should be planned to replace the IDDD in part or in its entirety.
2. CSF may be aspirated, and drug administered via lumbar puncture while awaiting IDDD revision, in accordance with the protocol.
3. If IDDD mechanical failure is confined to the port, its attachment to the catheter, or to the segment of catheter immediately adjacent to the port, proximal revision of the IDDD may be undertaken. In such an event, the old port and locking assembly is removed. New components are then implanted, leaving the original catheter in situ. However, the end of the catheter must be trimmed by at least one centimeter to restore a tight connection with the new port outlet tube. The patency of the apparatus must be ascertained intra-operatively, by aspirating CSF through the port, and flushing the device with sterile normal saline.

4. If IDDD mechanical failure is due to dislodgment of the catheter from the spinal canal, kinking at a location distal to the immediate vicinity of the port, or unresolved by proximal revision, the whole device must be replaced, following the instructions provided by Smith's Medical and the Shire training materials.

Note: All removed IDDDs must be returned to Smith's Medical for further analysis. Please refer to the Study Manual for instructions on the IDDD Return process. You should also contact Shire HGT.

Note: All IDDD related AEs (serious and nonserious) will be reported to Shire; all IDDD related SAEs will also be reported to Global Shire PVRM.

Drug Administration Following Device Revision:

1. If a full revision of the IDDD has been performed, an interval of 7 days is required before resuming administration of drug via IDDD.
2. If a proximal (ie, replacement of port only) revision of IDDD has been performed, drug administration through the IDDD can proceed immediately post-operatively.
3. In the event that the IDDD fails after 2 revisions in a 6-month time period, rhHNS may be administered and CSF collected by lumbar puncture for up to 5 successive months after which, IDDD re-implantation or revision must occur.

Appendix 4 Summary of Changes for Amendment 3

Clinical protocol HGT-SAN-067 has been revised from the previous version (Amendment 2, 13-Jan-2012) to update the study drug description to reflect a change in formulation. The protocol was also revised for the following purposes:

- Update the sponsor's contact phone number
- Clarify the timing of the neurological examination on days of study drug administration
- Clarify that Full Developmental Testing includes VABS-II
- Remove duplicative text describing the adverse events due to systemic exposure to rhHNS

The changes relative to Amendment 2 of the protocol (13-Jan-2012) are summarized below by section number; new or additional text is indicated in **Bold** and deleted text is indicated as ~~Strikethrough~~. Other sections affected by the same change are listed below each change.

Please note that only changes of substance are displayed here.

Change: The sponsor's contact phone number was updated.
Section impacted by this change: Title Page
Modified Text: Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 ~~USA~~**United States** [redacted]
No other sections were affected by this change.

Change: The text was updated to reflect a new study drug formulation with a higher concentration of the excipient polysorbate 20 and to correct a typo in the study drug name.
Section impacted by this change: Section 6.1.1 Study Drug
Modified Text: Recombinant human hepar~~i~~**a**n N-sulfatase (rhHNS) drug product formulation is a sterile solution for injection in single-use vials for intrathecal (IT) administration. It is formulated in an aqueous isotonic solution containing 15.0 mg/mL rhHNS in 145 mM sodium chloride, **0.02**~~0.005~~% (v/v) polysorbate 20, 5 mM sodium phosphate at pH 7.0.
No other sections were affected by this change.

Change: Text was added to clarify the timing of the neurological examination with respect to study drug administration.
Section impacted by this change: Section 7.16 Neurological Examination
The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.
Other sections affected by the same change: Section 8.2.1.2 Day 2 (±2 days) Assessments and Administration of rhHNS, Appendix 1 Schedule of Events

Change: Text was added to clarify that Full Developmental Testing includes VABS-II.
Section impacted by this change: Section 8.1 Screening Visit/Study Start Visit
Modified Text: • Full Neurodevelopmental assessments**, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments** performed prior to the administration of anesthesia)
Other sections affected by the same change: Section 8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose, Section 8.3 End of Study/Early Termination Procedures: Month 55, and Appendix 1 Schedule of Events

Change: Duplicative text describing the adverse events due to systemic exposure to rhHNS was removed.
Section impacted by this change: Section 7.22.1.1 Adverse Event
Deleted Text: ~~**POTENTIAL ADVERSE EVENTS: INTRATHECAL rhHNS**~~ ~~**Adverse Events Due To Systemic Exposure To rhHNS**~~ ~~Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion~~

~~will not be defined as infusion-related reactions.~~

POTENTIAL ADVERSE EVENTS: INTRATHECAL RECOMBINANT HUMAN HEPARAN N-SULFATASE

Adverse Events Due to Systemic Exposure to rhHNS

Although rhHNS is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other A**E**~~s~~ that occur prior to the infusion, along with A**E**~~s~~ associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

No other sections were affected by this change.

Appendix 5 Protocol Signature Page

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 Amendment 3
Final Date:	21 June 2010
Amendment 1 Date:	22 January 2011
Amendment 2 Date:	13 January 2012
Amendment 3 Date:	28 August 2012

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire HGT Medical Monitor

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

[redacted], MD
Printed Name

Appendix 6 The National Cancer Institute Common Toxicity Criteria

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
Device Names:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire and PORT-A-CATH® II Low Profile™ *Intrathecal Implantable Access System* (Smiths device)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter

Sponsor: Shire Human Genetic Therapies, Inc.
300 Shire Way
Lexington, MA 02421, United States

Medical Monitor: [redacted] MD, [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012
Amendment 3:	28 August 2012
Amendment 4:	3 May 2013

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421, United States

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)

Name of Active Ingredient:

rhHNS, HGT-1410

Name of Inactive Ingredient:

N/A

Names of Devices:

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

and

PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

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

Study Phase: I/II

Device, Intended Use

The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1410 indicated for intrathecal delivery intermittently over a long period of time.

Prior to approval of Amendment 4 patients were implanted with a PORT-A-CATH (Smith's device). After approval of Amendment 4 all PORT-A-CATH IDDDs requiring revision or replacement will be replaced with a SOPH-A-PORT at a time judged appropriate by the Investigator.

Study Objectives:

Primary Objective:

The primary objective of this study is:

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

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

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

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

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and/or CSF, and if possible, in serum and/or plasma.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with 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. Initially, patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study. Following approval of protocol Amendment 4, patients in the 10 mg group will have their dose increased to 45 mg per month.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of HGT-1410 in

Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments in the HGT-SAN-055 study. These assessments will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out. A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study). Note: X-rays may be performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy should be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055). Patients will also have X-ray examinations of the device performed at the EOS visit if the patient is to continue to receive intrathecal HGT-1410 beyond the end of the study.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria will be applied and will be based on the types and severity of adverse events (AEs)

reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 55). The EOS procedures will include 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.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of HGT-1410. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the operations manual (for PORT-A-CATH) or the IDDD Manual (for SOPH-A-PORT), which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), HGT-1410 will be administered via lumbar puncture (LP). Study drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

If there is no significant safety risk in the opinion of the Investigator, a non-functional IDDD may be 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 will be introduced for those patients requiring replacement or revision. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments are included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

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

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with HGT-1410.

Test Product; Dose; and Mode of Administration: Recombinant human heparan N-sulfatase (rhHNS, HGT-1410) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly). Patients assigned to the 10 mg monthly dose will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of the protocol amendment.

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment withHGT-1410.
5. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
6. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
7. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and

developmental testing procedures.
8. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
9. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
10. The patient has a history of a poorly controlled seizure disorder.
11. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
12. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
13. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
14. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
1. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
1. The patient has a known or suspected local or general infection
1. The patient is at risk of abnormal bleeding due to a medical condition or therapy
1. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
1. The patient has a functioning CSF shunt device
1. The patient has shown an intolerance to an implanted device

Duration of Treatment:

The study duration will be 4 years.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods: The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval (CI) around the mean will also be estimated and presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed Study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 4: 3 May 2013

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CNS	central nervous system
CO_2	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
CRIM	cross-reacting immunologic material
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
ERT	enzyme replacement therapy

EOS	end of study
EOW	every other week
EU	European Union
FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
H	High
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonization
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	instructions for use
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
L	Low
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MABC-2	Movement Assessment Battery for Children

MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MABC-2	Movement Assessment Battery for Children, Second Edition
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
NCI	National Cancer Institute
NCS	not clinically significant
PE	pressure-equalization
QoL	quality of life
Q4W	once per month
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
SOC	system organ class
TMF	Trial Master File
TX	treatment
UADE	unanticipated adverse device effect
US	United States
VABS-II	Vineland Adaptive Behavior Scales

WBC	white blood cell (count)
WHO-DD	WHO Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. Initially, the patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055. Following the analysis of data from HGT-SAN-055, patients in the lowest dose group will have their dose increased to 45 mg, as outlined in section 1.3, below.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is LSD caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A (MPS IIIA) results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtype A the most common of these.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1-3] In summary, MPS IIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5 - 7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8]

A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11, 12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the HGT-1410 clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an intrathecal drug delivery device (IDDD) due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13, 14, 16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L-Idurunonidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358).

This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by AE monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire HGT-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of HGT-1410 in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

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

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, HGT-1410 was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of HGT-1410 leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of HGT-1410 to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 µg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 µg dose given IT every-other-week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mgHGT-1410 given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, and the highest dose of HGT-1410 was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no HGT-1410-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin

relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene.

In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs,,HGT-1410 (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of HGT-1410 into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg HGT-1410 resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis and astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg HGT-1410 per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of HGT-1410 (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg HGT-1410 was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 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 patients who completed Study HGT-SAN-055 and elected to continue therapy with HGT-1410.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the end of study (EOS) evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will initially receive HGT-1410 at the same dose and schedule as they received in Study HGT-SAN-055. Patients assigned to 10 mg monthly will have their dose

increased to 45 mg monthly once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4. Based on analyses performed at the completion of Study HGT-SAN-055 a decline in the primary pharmacodynamic parameter, CSF heparan sulfate, was observed. This response to therapy was exhibited at all dose levels, however, the greatest impact was at the 2 higher dose levels. An effect on CSF heparan sulfate demonstrated in vivo activity of HGT-1410 in the target anatomical compartment. This effect is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410. As no apparent difference in safety profile was observed between the 3 dose groups, it was believed that the increase in the potential therapeutic benefit of the higher dose outweighed any potential increase in risks for this lowest dose group.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of HGT-1410 and PORT-A-CATH IDDD and SOPH-A-PORT Mini S device.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients 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.

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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.

2.3 Exploratory Objective

An exploratory objective of this study is:

- [redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

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

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

3.2 Secondary Endpoints

The secondary endpoints of this study are 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 inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine, plasma, and serum.
- Brain MRI and ABR, (also known as Brainstem Auditory Evoked Potentials).

3.3 SOPH-A-PORT Mini S Assessments

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of IT administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted HGT-1410 treatment. Patients will initially continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

- 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)

Patients assigned to Group 1 will initially receive 10 mg monthly but will have their dose increased to 45 mg monthly (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

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 patient received their first IT dose of HGT-1410 in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be

added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out.

A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055). If patients are to continue to receive HGT-1410 using the IDDD beyond the duration of this study, they will also have X-ray examinations of the device performed at the EOS visit, to document correct positioning.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 electronic case report forms (eCRFs). Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 55). The EOS procedures will include 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 X-ray examination of the device. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to administer HGT-1410. However, if a patient's PORT-A-CATH IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the PORT-A-CATH instructions for use (IFU), which describes the investigation and management of IDDD-related issues with this device. This will include possible partial revision or complete replacement of the PORT-A-CATH IDDD with a SOPH-A-PORT IDDD. For malfunctions involving the SOPH-A-PORT Mini S, site personnel will refer to the SOPH-A-PORT Instructions for Use (IFU). For either IDDD, a maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, HGT-1410

will be administered via LP. Drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of HGT-1410 via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT HGT-1410 administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in the HGT-SAN-067 study.

In order to traverse the blood-brain barrier, Shire HGT is evaluating HGT-1410 delivered directly to the CNS using an IDDD. The advantage of using an IDDD is that it obviates the need for multiple lumbar punctures for drug delivery. Drug products will be administered through this port or, if the IDDD is non functional, via lumbar puncture.

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

4.3 Study Duration and Dates

The study duration will be 4 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue HGT-1410 treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
3. The patient has a known or suspected local or general infection
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
6. The patient has a functioning CSF shunt device
7. The patient has shown an intolerance to an implanted device

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Intrathecal Drug Delivery Device

The PORT-A-CATH will continue to be used for the administration of drug product for each patient until such time as an IDDD replacement may be required. Following implementation of protocol Amendment 4, any replacements will be performed using the SOPH-A-PORT Mini S.

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

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

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

Further details are provided in the Instructions for Use.

6.1.3 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

HGT-1410 for IT administration will be provided by Shire HGT. HGT-1410 will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will initially receive the same dose of HGT-1410 they received 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)

Patients assigned to Group 1 will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

The study drug will be administered through an IDDD.

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

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

6.3 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT HGT-1410 dosing for safety assessments, designated Day 1, on each HGT-1410 treatment week, and if no safety concerns exist, will receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the Investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details). In the event of a non-functional IDDD, HGT-1410 may be administered by LP, for up to 5 successive months (see Section 6.3.3).

6.3.1 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for safety evaluation and biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling. Site personnel should refer to the operations manual for instructions on the use of topical anesthesia prior to accessing the IDDD reservoir.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the Study Operations Manual. CSF opening pressure will be measured whenever a LP is performed, and at the time of IDDD revision (partial or replacement). Additional CSF samples may be taken during this time.

6.3.2 Intrathecal Administration of HGT-1410

A visual examination of both the port and catheter track will be performed before each IT injection

HGT-1410 will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive HGT-1410 via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 4 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

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

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

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.3.3). The investigation and management of a malfunctioning IDDD is detailed in the PORT-A-CATH or SOPH-A-PORT IFUs. Partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.3.3 Administration of HGT-1410 via Lumbar Puncture

In the event of a non functional IDDD, HGT-1410 may be administered by LP, for up to 5 successive months. The performance of a LP is at the discretion of the Investigator.

If a LP is to be performed, the patient may require general anesthesia with appropriate airway management. Once the patient is anesthetized, a LP will be performed and a CSF sample will be obtained. Some cases may be managed with conscious sedation, if this is considered by the investigator to be adequate for the safe and expeditious performance of a LP.

6.4 Method of Assigning Patients to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with HGT-1410. Patients will initially receive the same dose of HGT-1410 they received in Study HGT-SAN-055. Patients assigned to Group 1 (10 mg once per month [Q4W]) will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

6.5 Blinding

Not applicable; as this trial is not blinded.

6.6 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Dictionary (WHO-DD).

6.7 Restrictions

6.7.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than HGT-1410 or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.7.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.7.3 Patient Activity Restrictions

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

6.8 Treatment Compliance

HGT-1410 is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.9 Packaging and Labeling

6.9.1 Drug Product

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of HGT-1410. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminium seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9.2 SOPH-A-PORT Mini S Access Port

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

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

6.10 Storage and Accountability

6.10.1 Investigational Product

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

All HGT-1410 study drug delivered to an Investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

6.10.2 Intrathecal Drug Delivery Device

6.10.2.1 PORT-A-CATH IDDD

Please refer to the operations manual for return instructions.

6.10.2.2 SOPH-A-PORT Mini S IDDD

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

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

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

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

6.11 Investigational Product Retention at Study Site

All HGT-1410 study drug delivered to an Investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory and/or Study Operations Manual.

7.2 Physical Examination

A physical examination of each patient will be performed as detailed in Appendix 1 Schedule of Events.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.9). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory and/or Study Operations Manual.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.7.4 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.7.4.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.7.4.2 Urine Heparan Sulfate and Heparan Sulfate Derivatives

A urine sample will be collected for the determination of heparan sulfate and heparan sulfate derivatives and the analysis will be performed at Shire HGT or designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.5 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.5.1, 7.7.5.2, and 7.7.5.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or RNA may become used as they become available in the future.

7.7.5.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.5.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire HGT laboratories.

7.7.5.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of anti-rhHNS antibodies at Shire HGT or Shire HGT designated laboratories.

7.7.5.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of MPS exploratory biomarkers at Shire HGT laboratories.

7.7.6 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual to be provided by Shire HGT.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Device Data

[redacted]

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. After full approval of protocol Amendment 4, all IDDD replacements will be made with the SOPH-A-PORT IDDD. If the IDDD device is a

PORT-A-CATH IDDD, it will be replaced by a SOPH-A PORT IDDD. Management details for the PORT-A- CATH IDDD or for the SOPH-A PORT IDDD are provided in the respective device's IFU. Procedures for implantation are detailed in the relevant device's Instructions for Use Manual and in the training materials provided by Shire HGT. The patient will be under general anesthesia for this procedure. The CSF opening pressure will be recorded when the intrathecal space is first entered at the time of the IDDD re-implantation. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly, and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the Study Operations Manual).

A post-operative check of the IDDD and incision will be performed on Day 4 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Device Related Study Procedures

7.13.1 IDDD Implantation or Revision Procedures

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

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

Details of the implantation/revision and malfunctions/failure for the SOPH-A-PORT will be documented on the patient's eCRF.

7.13.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative x-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, as needed, throughout the study. If the patient is to receive intrathecal HGT-1410 beyond the end of the study, an X-ray will be performed at the end of the study to verify that the IDDD is in the correct position. At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional x-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray may be performed to assess the potential cause of malfunction

7.13.3 CSF Sampling Procedure

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

7.13.4 Device Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's IFU due to a device-related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

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

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

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

If the IT space is not accessible via the IDDD, study drug may be administered by LP up to 5 times.

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

7.14 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision or replacement is done.

7.15 Dispensing Study Drug

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. HGT-1410 will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, HGT-1410 may be administered via LP. See Section 6.3.3 for details.

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

7.16 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.17 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

7.18 Anti-rhHNS Antibody, Heparan Sulfate, and Heparan Sulfate Derivative Determination

Blood samples will be collected and evaluated at Shire HGT laboratories for the determination of anti-rhHNS antibodies, and plasma and serum heparan sulfate and heparan sulfate derivatives. Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual.

7.19 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they

become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1. Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2. Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.20 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.21 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.21.1, 7.21.2, and 7.21.3.

7.21.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age.

7.21.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being.

7.21.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.22 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.23 Adverse Events

7.23.1 Definitions of Adverse Events and Serious Adverse Events

7.23.1.1 Adverse Event

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

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

Throughout the study, the Investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to study drug. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All AEs should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of HGT-1410. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to HGT-1410 caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of HGT-1410 to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal HGT-1410 therapy to date.

7.23.1.2 Potential Adverse Events: Intrathecal recombinant human heparan N-sulfatase

ADVERSE EVENTS RELATED TO THE DIRECT DELIVERY OF HGT-1410 TO THE CNS THROUGH INTRATHECAL ADMINISTRATION

Examples of AEs observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory parathesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time

ADVERSE EVENTS DUE TO SYSTEMIC EXPOSURE TO HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

7.23.1.3 IDDD-related Adverse Events

IDDD ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A list of the more common IDDD AEs is included in Appendix 3.

If the patient is admitted to the hospital in association with an IDDD event (eg for subsequent revision or replacement) the surgery will be recorded as a SAE.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS

Examples of AEs related to surgical procedures include, but are not limited to, the following: IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal.

IT ADMINISTRATION PROCESS ADVERSE EVENTS

In studies that include administration of investigational drug with an IDDD, potential AEs related to the IT Administration process include AEs that are caused by anesthesia during drug

administration, drug administration issues (eg, extravasation during infusion or hematoma due to Huber needle), etc.

7.23.1.4 Serious Adverse Event

1. A serious AE (SAE) is any AE occurring at any dose of investigational drug or at any procedure that results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization. Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s). *Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs."*

2. Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21CFR812.3[s] or other regulatory requirements, as applicable).

7.23.2 Device-Associated Definitions

7.23.2.1 Device Revision (Partial and Full)

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

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

7.23.2.2 Device Malfunction

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

7.23.2.3 Device Failure

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

7.23.3 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page. Adverse events are graded as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3. Adverse Event Severity

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

7.23.4 Relatedness of Adverse Events and Serious Adverse Events

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

Table 7-4. Adverse Event Relatedness

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

7.23.5 Procedures for Recording and Reporting Adverse Events

7.23.5.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE regardless of relationship to investigational product, device, device surgical procedure, or IT administration process that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire HGT Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study procedure. The Investigator will promptly supply all information identified and requested by the Sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device, or procedure.

The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted] **United Kingdom OR**
United States FAX: [redacted]
Email: [redacted]
AND
Shire HGT Medical Monitor:
FAX: [redacted] **(United States)**

The Investigator may also call the Medical Monitor directly (optional):

Shire HGT Medical Monitor: [redacted] **MD**
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted] **(24 hour access)**
Email: [redacted]
AND
Clinical Project Manager CC'd: [redacted]

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

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

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

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication

7.23.5.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. The relationship of each AE to study medication must be recorded. In addition AEs may be considered to be related to the IDDD, the IDDD surgical procedure, or the IT administration process. Since the AE may be deemed to be related to more than one of these factors, as many of these IDDD-related options as apply should be indicated on the eCRF.

7.23.5.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The Investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire HGT Medical Monitor (see Section 7.23.5.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The Investigator or other physician in attendance in such an emergency must contact the Shire HGT Medical Monitor as soon as possible.

The Investigator, along with the Shire HGT Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.24 Abuse, Overdose and Medication Errors

Abuse, misuse, overdose or medication error must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.23.

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed **by the protocol)**
- **Overdose –** Overdosage with adverse clinical consequences is not anticipated with the use of HGT-1410. Additionally, HGT-1410 will be given in a clinical setting by a health care provider.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

7.25 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered by the sponsor to be possibly, probably, or definitely related to study drug **or the IDDD**, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered by the sponsor to be possibly, probably, or definitely related to the study drug **or the IDDD**, then the site will be instructed to halt further HGT-1410 administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.26 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of HGT-1410 throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of HGT-1410. The clinical site's local laboratory will analyze and report all pregnancy testing

results. If a pregnancy test is positive the patient will be discontinued from the study, and the Investigator must contact the Shire HGT Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.27 Removal of Patients from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a

previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.28 Other Study Procedures

This section is not applicable.

7.29 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last HGT-1410 administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of HGT-1410 in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal HGT-1410 dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
- ABR
- MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments performed prior to the administration of anesthesia)
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments

Patients will receive HGT-1410 IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection. Note: Patients will not receive study drug if the pre-dose CSF contains >100 WBC per cubic millimeter.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs
- Hematology
- Serum chemistry
- Urinalysis
- Pregnancy testing (applicable females only)
- Neurological examination (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal HGT-1410 treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, AND 54

- Head circumference
- Visual and hearing assessments
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and /or serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR
- MRI of the head
- Full neurodevelopmental testing, including VABS-II (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of HGT-1410

Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

- Physical examination
- ECG (performed following IT study drug injection)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- HGT-1410 IT injection (Day 2 ±2 days)
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

8.3 End of Study/Early Termination Procedures: Month 55

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of HGT-1410.

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, expanded access, commercially available).

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR (unless performed at Month 54)
- MRI of the head (unless performed at Month 54)
- CSF sample collection (unless performed at Month 54)
- Neurological examination
- Full neurodevelopmental testing, including VABS-II
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QOL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments
- X-ray of device, if the patient is to continue to receive intrathecal HGT-1410 beyond the end of the study

All patients who discontinue the study early will have their IDDD removed.

Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 56

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire HGT or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of HGT-1410 in patients with MPS IIIA. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables, and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

No a priori hypotheses will be tested. Exploratory hypotheses may emerge from the data analysis, in which case, appropriate testing methods will be applied and specified in the statistical analysis plan.

There are no formal hypotheses associated with the evaluation of the safety and performance of the IDDD device (SOPH-A-PORT Mini S). All analyses of device safety and performance will be descriptive and no statistical testing will be performed. Device related analyses will be based on patients for whom the device implant procedure was performed and are described in the sections below.

10.2 Determination of Sample Size

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

10.3 Analysis Populations

The primary analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. This population will be used to perform both safety and efficacy analyses. The collection of detailed data pertaining to the SOPH-A-PORT mini S will permit device-related analyses to be conducted in the subset of patients in the primary analysis population who had the SOPH-A-PORT Mini S implant procedure performed**.**

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of AEs, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients who had an IDDD surgical procedure and/or received administration of HGT-1410 will be included in the safety analysis.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each dose group, the number and percentage of patients having any AE, having an AE in system organ class, and having each individual AE. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events , defined as all AEs from the time of the surgery for IDDD implantation to the last follow up contact, ie, 30 days after the last HGT-1410 administration, (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication/procedure.

Treatment-emergent AEs deemed related to HGT-1410 administration will be summarized separately.

IDDD, and procedure-related AEs will be summarized within system organ class by preferred term. IDDD and procedure-related AEs will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure (including post-implant infections) and IT administration process. These summaries will be presented by device and overall, as appropriate.

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis and CSF) results will be presented in summary tables by evaluation visit. Changes from baseline will be summarized for each post-baseline visit. Each laboratory result will be categorized as a patient having had (1) an Abnormal and Clinically Significant (CS) value at any time, (2) no CS values at any time but had at least one Abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any time 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.

The observed values and changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

The observed values and changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by number and percentage of positive and negative specimens by evaluation visit, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.2 Other Observations Related to Safety

10.6.2.1 IDDD Performance

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

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

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

10.6.3 Secondary Analysis

10.6.3.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of HGT-1410 administration on QoL measures will be examined by presenting mean change from baseline by dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.3.2 Pharmacodynamic Analyses

To determine the effects of HGT-1410 administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparan sulfate reduction (in CSF and urine) will be examined using mean change and the corresponding 95% confidence interval. The concentration of inflammatory cytokines in serum and CSF will also be examined. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

The planned analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

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

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

Before Shire HGT initiates the trial (ie, obtains informed consent [assent if applicable] from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available to Shire HGT or their designee:

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire HGT. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire HGT.

11.8 Device Failure Adjudication Process

The final cause for device failures will be adjudicated by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire HGT and the Investigators. In addition, a decision on the part of Shire HGT to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.7.6).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

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Appendix 1 Schedule of Events

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**
Informed Consent/Enrollment		●				
Physical Examination	●	●	●		●	
Height and Weight	●	●			●	
Head Circumference	●			●	●	
Visual and Hearing Assessment				●	●	
ECG	●		●[b]		●	
Vital Signs	●	●	●		●	
Hematology	●	●			●	
Serum Chemistry	●	●			●	
Pregnancy Testing[n]	●	●				
Urinalysis	●	●			●	
Leukocyte pellet preparation[o]	●					
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Plasma and serum Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[l]	●			●	●	
Auditory Brainstem Response (ABR)	●			●	●[p]	
MRI of the Head	●			●	●[p]	
CSF Sample Collection[m]	●		●[c]		●[c, p]	
HGT-1410 dosing: every 28 (±7) days [d, g,]			●			
Neurological Examination[h]	●	●	●		●	
Full Neurodevelopmental Testing[i]	●			●	●	
Children's Sleep Habits Rating Scale	●			●	●	
Child Health Questionnaire-50	●			●	●	

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**
Child Health Questionnaire-87	●			●	●	
Infant Toddler QOL Questionnaire	●			●	●	
Concomitant Medications, Therapies, and Procedures	●	●	●		●	●
Adverse Event Monitoring	●	●	●		●	●
X-ray examination of device (if treatment is to continue beyond end of study)					●	
Removal of IDDD				●[q]	●[q]	

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; EOS = end of study ; ECG = electrocardiogram; IT = intrathecal; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as presented here at Month 54, corresponds to Month 48 in HGT-SAN-067, but represents a total of 54 months of study treatment (48 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] CSF samples will be obtained according to the process with in the study operations manual). An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of HGT-1410 and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or a LP may be performed (can occur up to 5 times in a 6 month period).

[d] Patients may be discharged as early as 4 hours post HGT-1410 infusion (ie, on Day 2) when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] The neurological exam should not occur sooner than 4 hours after administration of study drug or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

[i] Full neurodevelopmental testing includes an assessment with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

[j] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[k] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled HGT-1410 IT dose.

[l] Blood sample drawn before IT injection of HGT-1410.

[m] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**

[n] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[o] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

[P] These assessments are not to be performed at an EOS visit conducted at Month 55 if they were performed at the Month 54 visit

[q] The IDDD will be removed at the Month 54 visit, or at the EOS visit if the patient discontinues the study prior to the Month 54 visit

Appendix 2 Neurodevelopmental and Behavioral Assessments

Table 4-1 and Table 4-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table 4-1. Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table 4-2. Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child’s abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III) [23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II) [24]

Purpose:

The KABC-II measures a child’s cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery’s results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS) [5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Expected Adverse Device Effects

Procedure-Related Complications

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

Intrathecal Access Complications

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

System-Related Complications

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

Appendix 4 Protocol Amendment Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol HGT-SAN-067 has been amended to include language to indicate that patients in the lowest dose group (10 mg Q4W) are to have the dose increased to that of the mid-dose, ie, 45 mg at the first visit following the full approval of this protocol. A decline in the primary pharmacodynamic parameter, CSF heparan sulfate, was observed in data collected during the 6-month study, HGT-SAN-055. This response to therapy was exhibited at all dose levels, however, the greatest impact was at the 2 higher dose levels An effect on CSF heparan sulfate demonstrated in vivo activity of HGT-1410 in the target anatomical compartment, and is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410. As no apparent differences in safety profile was observed between the 3 dose groups it was believed that the increase in the potential therapeutic benefit of the higher dose outweighed any potential increase in risks for this lowest dose group.

The protocol has also been amended to reduce the number of hours a patient is monitored at the site after administration of HGT-1410 from 8 hours to 4 hours. The monitoring time after each administration of HGT-1410 was reconsidered based on experience with IT administration of HGT-1410, ie a lack of injection-associated safety issues occurring between 4 and 8 hours after administration.

The protocol has also been amended to include a description of a new intrathecal drug delivery device, the SOPH–A–PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire. In light of the higher than expected complications experienced with the previous IDDD the SOPH-A-PORT Mini S device will be introduced for those patients requiring replacement or revision. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments are included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including changes for consistency and clarity), and updates to the list of abbreviations and cross-references are not reflected in the change summary.

Previous Amendment: Amendment 3; 28 August 2012

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: Dose of the 10 mg Q4W group increased to 45 mg Q4W
Section impacted by this change: Section 6.4
Patients will **initially** receive the same dose of HGT-1410 they received in Study HGT-SAN-055. **Patients assigned to Group 1 (10 mg once per month [Q4W]) will have their dose increased to 45 mg once per month (Q4W) at the first administration of**

HGT-1410 following full approval of the protocol amendment.
Other sections impacted by this change: Synopsis; Sections 1.3; 4.1;and 6.2

Change: The number of hours a patient is monitored in the clinic after each administration of HGT-1410 is reduced from 8 hours to xx
Section impacted by this change: Section 4.1;
Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study centre for at least **4** hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.
Other sections impacted by this change: Synopsis; Sections 6.3; 6.3.2; and 8.2; Appendix 1 Schedule of Events

Change: Introduction of the SOPH-A-PORT to replace the PORT-A-CATH for those patients requiring a replacement or revision.
Section impacted by this change: Section 1.1
In light of the higher than expected complications experienced with the PORT-A-CATH IDDD, due primarily to device design features, the SOPH-A-PORT Mini S device will be introduced for those patients requiring replacement or revision. This new device was designed with the intention of minimizing the complications encountered with the PORT-A-CATH IDDD device. Provisions are made in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.
Other sections impacted by this change: Sections 1.3; 4.2; 6.1.2; and 6.9.2

Change: Three categories of adverse events associated with the device are defined.
Section impacted by this change:
7.23.1.3 IDDD-related Adverse Events **IDDD ADVERSE EVENTS** **Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A list of the more common IDDD AEs is included in Appendix 4.** **DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS** **Examples of AEs related to surgical procedures include, but are not limited to, the following: IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD**

removal, and delayed re-implantation after previous IDDD removal. **IT ADMINISTRATION PROCESS ADVERSE EVENTS** **In studies that include administration of investigational drug with an IDDD, potential AEs that are caused by anesthesia during drug administration, drug administration issues (eg, extravasation during infusion or hematoma due to Huber needle), etc.**
Other sections impacted by this change: None

Change: Severity grading of device-associated adverse events specified
Section impacted by this change: Section7.23.3
The severity of all AEs/SAEs should be recorded on the appropriate eCRF page. **Adverse events are to be graded as Grade 1, 2, or 3. All other AEs are graded** as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.
Other sections impacted by this change: None

Change: Device revisions and malfunctions defined
Section impacted by this change: Section 7.23.2
7.23.2 Device-Associated Definitions **7.23.2.1 Device Revisions (Partial and Full)** **Partial device revision: surgical revision/replacement of one or more component(s) of the device; other component(s) of the original device remain implanted and are not affected (eg, port revision)** **Full device revision: the device is removed (explanted) in its entirety and a completely new device is implanted.** **7.23.2.2 Device Malfunction** **The device does not perform as intended, based on the description in the device's IFU, but does not require either a partial or full device revision.** **7.23.2.3 Device Failure** **The device irreversibly fails to perform as intended and requires either a partial or full device revision or removal.**
Other sections impacted by this change: None

Change: Clarification that AEs may be considered related to the IDDD in addition to the study drug
Section impacted by this change: Section 7.23.5.2
The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. The relationship of each AE to study medication must be recorded. In addition AEs may be considered to be related to the IDDD, the IDDD surgical procedure or the IT administration process. As many of these IDDD-related options as apply will be indicated on the eCRF.
Other sections impacted by this change: None

Change: Standard Abuse, Overdose and Medication Error
Section impacted by this change: Section 7.24
7.24 **Abuse, Overdose and Medication Error** • Abuse – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness) • Misuse – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed by the protocol) • Overdose – Overdosage with adverse clinical consequences is not anticipated with the use of HGT-1410. Additionally, HGT-1410 will be given in a clinical setting by a health care provider. • Medication Error – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.
Other sections impacted by this change: None

Change: Clarifications were made within the statistical analysis section. Section 10.1 clarified exploratory hypotheses, Section 10.3 clarified that SOPH-A-PORT device-related analyses would be conducted in the subset of patients in the primary analysis population who had **the SOPH-A-PORT Mini S implant procedure performed, and Section** 10.6.1.1**. detailed analyses for IDDD-related AEs.**
Section impacted by this change: Sections 10.1, 10.3 and 10.6.1.1
•
Other sections impacted by this change: None

Change: Modifications to the Statistical Methodology Section, particularly the analysis of device-related AEs
Section impacted by this change: Section 10.6.2.1
10.6.2.1 **IDDD Performance**

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

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

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

Other sections impacted by this change: Sections 10.3; and 10.6.1.1

Change: Clarification that an x-ray of the device was to be performed at the EOS visit. This had been included in Section 7.13.2 but not other appropriate sections.

Section impacted by this change: Section 4.1

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 55). The EOS procedures will include 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 X-ray examination of the device.**

Other sections impacted by this change: Synopsis, Section 8.3, Appendix 1 Schedule of Events

Change: Implementation of a Device Failure Adjudication Process

Section impacted by this change: Section 11.8

11.8 **Device Failure Adjudication Process**

The final cause for device failures will be adjudicated by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

Other sections impacted by this change: None

Change: Addition of a list of expected adverse device effects
Section impacted by this change: Appendix 3
All Appendix 3 is new.

Appendix 5 Protocol Signature Page

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 Amendment 4

Final Date: 21 June 2010

Amendment 1 Date: 22 January 2011

Amendment 2 Date: 13 January 2012

Amendment 3 Date: 28 August 2012

Amendment 4 Date: 3 May 2013

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire HGT Medical Monitor

[redacted]
Signature **Date**

[redacted], MD
Printed Name

Appendix 6 The National Cancer Institute Common Terminology Criteria version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
Device Names:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire and PORT-A-CATH® II Low Profile™ *Intrathecal Implantable Access System* (Smiths device)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter

Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421, United States
Medical Monitor:	[redacted] MD, [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012
Amendment 3:	28 August 2012
Amendment 4:	3 May 2013
Amendment 5:	17 January 2014

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421, United States

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)

Name of Active Ingredient:

rhHNS, HGT-1410

Name of Inactive Ingredient:

N/A

Names of Devices:

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

and

PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

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

Study Phase: I/II

Device, Intended Use

The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1410 indicated for intrathecal delivery intermittently over a long period of time.

Prior to approval of Amendment 4 patients were implanted with a PORT-A-CATH (Smith's device). After approval of Amendment 4 all PORT-A-CATH IDDDs requiring revision or replacement will be replaced with a SOPH-A-PORT at a time judged appropriate by the Investigator.

Study Objectives:

Primary Objective:

The primary objective of this study is:

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

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

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

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

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life questionnaires, and Children's Sleep Habits Rating Scale.
- Concentration of inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine and/or CSF, and if possible, in serum and/or plasma.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with 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. Initially, patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study. Following approval of protocol Amendment 4, patients in the 10 mg group will have their dose increased to 45 mg per month.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of HGT-1410 in

Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments in the HGT-SAN-055 study. These assessments will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out. A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study). Note: X-rays may be performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy should be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055). Patients will also have X-ray examinations of the device performed at the EOS visit if the patient is to continue to receive intrathecal HGT-1410 beyond the end of the study.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria will be applied and will be based on the types and severity of adverse events (AEs)

reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 55). The EOS procedures will include 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.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of HGT-1410. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the operations manual (for PORT-A-CATH) or the IDDD Manual (for SOPH-A-PORT), which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), HGT-1410 will be administered via lumbar puncture (LP). Study drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

If there is no significant safety risk in the opinion of the Investigator, a non-functional IDDD may be 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 will be introduced for those patients requiring replacement or revision. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments are included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

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

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with HGT-1410.

Test Product; Dose; and Mode of Administration: Recombinant human heparan N-sulfatase (rhHNS, HGT-1410) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly). Patients assigned to the 10 mg monthly dose will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of the protocol amendment.

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment withHGT-1410.
5. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
6. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
7. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and

developmental testing procedures.
8. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
9. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
10. The patient has a history of a poorly controlled seizure disorder.
11. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
12. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
13. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
14. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
1. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
1. The patient has a known or suspected local or general infection
1. The patient is at risk of abnormal bleeding due to a medical condition or therapy
1. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
1. The patient has a functioning CSF shunt device
1. The patient has shown an intolerance to an implanted device

Duration of Treatment:

The study duration will be 4 years.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods: The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval (CI) around the mean will also be estimated and presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed Study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 5: 17 January 2014

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CNS	central nervous system
CO_2	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
CRIM	cross-reacting immunologic material
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture

Abbreviation	Definition
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
EU	European Union
FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonization
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	instructions for use
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MABC-2	Movement Assessment Battery for Children

Abbreviation	Definition
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MABC-2	Movement Assessment Battery for Children, Second Edition
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
NCI	National Cancer Institute
NCS	not clinically significant
PE	pressure-equalization
QoL	quality of life
Q4W	once per month
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UADE	unanticipated adverse device effect
US	United States
VABS-II	Vineland Adaptive Behavior Scales

Abbreviation	Definition
WBC	white blood cell (count)
WHO-DD	WHO Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. Initially, the patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055. Following the analysis of data from HGT-SAN-055, patients in the lowest dose group will have their dose increased to 45 mg, as outlined in Section 1.3, below.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is LSD caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A (MPS IIIA) results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtype A the most common of these.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1-3] In summary, MPS IIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5 - 7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8]

A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11, 12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the HGT-1410 clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an intrathecal drug delivery device (IDDD) due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13, 14, - 16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L-Idurunonidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358).

This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse event (AE) monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire HGT-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of HGT-1410 in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

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

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, HGT-1410 was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of HGT-1410 leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of HGT-1410 to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 μg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 μg dose given IT every other week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mgHGT-1410 given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, and the highest dose of HGT-1410 was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no HGT-1410-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin

relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene.

In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs, HGT-1410 (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of HGT-1410 into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg HGT-1410 resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis and astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg HGT-1410 per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of HGT-1410 (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg HGT-1410 was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 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 patients who completed Study HGT-SAN-055 and elected to continue therapy with HGT-1410.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the end of study (EOS) evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will initially receive HGT-1410 at the same dose and schedule as they received in Study HGT-SAN-055. Patients assigned to 10 mg monthly will have their dose

increased to 45 mg monthly once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4. Based on analyses performed at the completion of Study HGT-SAN-055 a decline in the primary pharmacodynamic parameter, CSF heparan sulfate, was observed. This response to therapy was exhibited at all dose levels, however, the greatest impact was at the 2 higher dose levels. An effect on CSF heparan sulfate demonstrated in vivo activity of HGT-1410 in the target anatomical compartment. This effect is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410. As no apparent difference in safety profile was observed between the 3 dose groups, it was believed that the increase in the potential therapeutic benefit of the higher dose outweighed any potential increase in risks for this lowest dose group.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of HGT-1410 and PORT-A-CATH IDDD and SOPH-A-PORT Mini S device.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients 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.

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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.

2.3 Exploratory Objective

An exploratory objective of this study is:

- [redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

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

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

3.2 Secondary Endpoints

The secondary endpoints of this study are 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 inflammatory cytokines in serum and CSF.
- Concentration of safety and potential surrogate efficacy biomarkers in CSF, urine, and serum.
- Concentration of heparan sulfate and heparan sulfate derivatives in urine, plasma, and serum.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), (also known as Brainstem Auditory Evoked Potentials).

3.3 SOPH-A-PORT Mini S Assessments

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of IT administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted HGT-1410 treatment. Patients will initially continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

- 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)

Patients assigned to Group 1 will initially receive 10 mg monthly but will have their dose increased to 45 mg monthly (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

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 patient received their first IT dose of HGT-1410 in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be

added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out.

A MRI of the head and ABR testing will be performed at Months 12, 24, 36, and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055). If patients are to continue to receive HGT-1410 using the IDDD beyond the duration of this study, they will also have X-ray examinations of the device performed at the EOS visit, to document correct positioning.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 eCRFs. Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 55). The EOS procedures will include 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 X-ray examination of the device. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit (ie, Month 56) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to administer HGT-1410. However, if a patient's PORT-A-CATH IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the PORT-A-CATH Instructions for Use (IFU), which describes the investigation and management of IDDD-related issues with this device. This will include possible partial revision or complete replacement of the PORT-A-CATH IDDD with a SOPH-A-PORT IDDD. For malfunctions involving the SOPH-A-PORT Mini S, site personnel will refer to the SOPH-A-PORT IFU. For either IDDD, a maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, HGT-1410 will be

administered via lumbar puncture (LP). Drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of HGT-1410 via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT HGT-1410 administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in the HGT-SAN-067 study.

In order to traverse the blood-brain barrier, Shire HGT is evaluating HGT-1410 delivered directly to the CNS using an IDDD. The advantage of using an IDDD is that it obviates the need for multiple lumbar punctures for drug delivery. Drug products will be administered through this port or, if the IDDD is non functional, via lumbar puncture.

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

4.3 Study Duration and Dates

The study duration will be 4 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue HGT-1410 treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
3. The patient has a known or suspected local or general infection
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
6. The patient has a functioning CSF shunt device
7. The patient has shown an intolerance to an implanted device

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Intrathecal Drug Delivery Device

The PORT-A-CATH will continue to be used for the administration of drug product for each patient until such time as an IDDD replacement may be required. Following implementation of protocol Amendment 4, any replacements will be performed using the SOPH-A-PORT Mini S.

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

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

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

Further details are provided in the Instructions for Use.

6.1.3 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

HGT-1410 for IT administration will be provided by Shire HGT. HGT-1410 will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will initially receive the same dose of HGT-1410 they received 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)

Patients assigned to Group 1 will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

The study drug will be administered through an IDDD.

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

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

6.3 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT HGT-1410 dosing for safety assessments, designated Day 1, on each HGT-1410 treatment week, and if no safety concerns exist, will receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the Investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details). In the event of a non-functional IDDD, HGT-1410 may be administered by LP, for up to 5 successive months (see Section 6.3.3).

6.3.1 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for clinical laboratory evaluation and potential biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling. Site personnel should refer to the operations manual for instructions on the use of topical anesthesia prior to accessing the IDDD reservoir.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the Study Operations Manual. CSF opening pressure will be measured whenever a LP is performed, and at the time of IDDD revision (partial or replacement). Additional CSF samples may be taken during this time.

6.3.2 Intrathecal Administration of HGT-1410

A visual examination of both the port and catheter track will be performed before each IT injection

HGT-1410 will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive HGT-1410 via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 4 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

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

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

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.3.3). The investigation and management of a malfunctioning IDDD is detailed in the PORT-A-CATH or SOPH-A-PORT IFUs. Partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.3.3 Administration of HGT-1410 via Lumbar Puncture

In the event of a nonfunctional IDDD, HGT-1410 may be administered by LP, for up to 5 successive months. The performance of a LP is at the discretion of the Investigator.

If a LP is to be performed, the patient may require general anesthesia with appropriate airway management. Once the patient is anesthetized, a LP will be performed and a CSF sample will be obtained. Some cases may be managed with conscious sedation, if this is considered by the investigator to be adequate for the safe and expeditious performance of a LP.

6.4 Method of Assigning Patients to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with HGT-1410. Patients will initially receive the same dose of HGT-1410 they received in Study HGT-SAN-055. Patients assigned to Group 1 (10 mg once per month [Q4W]) will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

6.5 Blinding

Not applicable; as this trial is not blinded.

6.6 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Dictionary (WHO-DD).

6.7 Restrictions

6.7.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than HGT-1410 or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.7.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.7.3 Patient Activity Restrictions

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

6.8 Treatment Compliance

HGT-1410 is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.9 Packaging and Labeling

6.9.1 Drug Product

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of HGT-1410. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminium seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9.2 SOPH-A-PORT Mini S Access Port

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

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

6.10 Storage and Accountability

6.10.1 Investigational Product

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

All HGT-1410 study drug delivered to an Investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

6.10.2 Intrathecal Drug Delivery Device

6.10.2.1 PORT-A-CATH IDDD

Please refer to the operations manual for return instructions.

6.10.2.2 SOPH-A-PORT Mini S IDDD

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

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

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

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

6.11 Investigational Product Retention at Study Site

All HGT-1410 study drug delivered to an Investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory and/or Study Operations Manual.

7.2 Physical Examination

A physical examination of each patient will be performed as detailed in Appendix 1 Schedule of Events.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.9). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory and/or Study Operations Manual.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.7.4 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.7.4.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.7.4.2 Urine Heparan Sulfate and Heparan Sulfate Derivatives

A urine sample will be collected for the determination of heparan sulfate and heparan sulfate derivatives and the analysis will be performed at Shire HGT or designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.5 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.5.1, 7.7.5.2, and 7.7.5.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or ribonucleic acid RNA may become used as they become available in the future.

7.7.5.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.5.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire HGT laboratories.

7.7.5.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of anti-rhHNS antibodies at Shire HGT or Shire HGT designated laboratories.

7.7.5.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory and/or Study Operations Manual for subsequent determination of MPS exploratory biomarkers at Shire HGT laboratories.

7.7.6 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual to be provided by Shire HGT.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Device Data

[redacted]

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. After full approval of protocol Amendment 4, all IDDD replacements will be made with the SOPH-A-PORT IDDD. If the IDDD device is a PORT-A-CATH IDDD, it will be replaced by a SOPH-A PORT IDDD. Management details for

the PORT-A- CATH IDDD or for the SOPH-A PORT IDDD are provided in the respective device's IFU. Procedures for implantation are detailed in the relevant device's Instructions for Use Manual and in the training materials provided by Shire HGT. The patient will be under general anesthesia for this procedure. The CSF opening pressure will be recorded when the intrathecal space is first entered at the time of the IDDD re-implantation. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly, and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the Study Operations Manual).

A post-operative check of the IDDD and incision will be performed on Day 4 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Device Related Study Procedures

7.13.1 IDDD Implantation or Revision Procedures

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

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

Details of the implantation/revision and malfunctions/failure for the SOPH-A-PORT will be documented on the patient's eCRF.

7.13.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative x-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, as needed, throughout the study. If the patient is to receive intrathecal HGT-1410 beyond the end of the study, an X-ray will be performed at the end of the study to verify that the IDDD is in the correct position. At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional x-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray may be performed to assess the potential cause of malfunction

7.13.3 CSF Sampling Procedure

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

7.13.4 Device Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's IFU due to a device-related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

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

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

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

If the IT space is not accessible via the IDDD, study drug may be administered by LP up to 5 times.

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

7.14 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision or replacement is done.

7.15 Dispensing Study Drug

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. HGT-1410 will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, HGT-1410 may be administered via LP. See Section 6.3.3 for details.

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

7.16 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.17 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

7.18 Anti-rhHNS Antibody, Heparan Sulfate, and Heparan Sulfate Derivative Determination

Blood samples will be collected and evaluated at Shire HGT laboratories for the determination of anti-rhHNS antibodies, and plasma and serum heparan sulfate and heparan sulfate derivatives. Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory and/or Study Operations Manual.

7.19 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they

become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.20 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.21 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.21.1, 7.21.2, and 7.21.3.

7.21.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age.

7.21.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being.

7.21.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.22 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.23 Adverse Events

7.23.1 Definitions of Adverse Events and Serious Adverse Events

7.23.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

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

Throughout the study, the Investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to study drug. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All AEs should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of HGT-1410. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to HGT-1410 caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of HGT-1410 to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal HGT-1410 therapy to date.

7.23.1.2 Potential Adverse Events: Intrathecal recombinant human heparan N-sulfatase

ADVERSE EVENTS RELATED TO THE DIRECT DELIVERY OF HGT-1410 TO THE CNS THROUGH INTRATHECAL ADMINISTRATION

Examples of AEs observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory parathesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time

ADVERSE EVENTS DUE TO SYSTEMIC EXPOSURE TO HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

7.23.1.3 IDDD-related Adverse Events

IDDD ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A list of the more common IDDD AEs is included in Appendix 3.

If the patient is admitted to the hospital in association with an IDDD event (eg for subsequent revision or replacement) the surgery will be recorded as a SAE.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS

Examples of AEs related to surgical procedures include, but are not limited to, the following: IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD removal.

IT ADMINISTRATION PROCESS ADVERSE EVENTS

In studies that include administration of investigational drug with an IDDD, potential AEs related to the IT Administration process include AEs that are caused by anesthesia during drug administration, drug administration issues (eg, extravasation during infusion or hematoma due to Huber needle), etc.

7.23.1.4 Serious Adverse Event

1. A serious AE (SAE) is any AE occurring at any dose of investigational drug or at any procedure that results in any of the following outcomes:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization. Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s). *Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs."*

2. Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21CFR812.3[s] or other regulatory requirements, as applicable).

7.23.2 Device-Associated Definitions

7.23.2.1 Device Revision (Partial and Full)

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

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

7.23.2.2 Device Malfunction

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

7.23.2.3 Device Failure

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

7.23.3 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page. Adverse events are graded as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3 Adverse Event Severity

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

7.23.4 Relatedness of Adverse Events and Serious Adverse Events

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

Table 7-4 Adverse Event Relatedness

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

7.23.5 Procedures for Recording and Reporting Adverse Events

7.23.5.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE regardless of relationship to investigational product, device, device surgical procedure, or IT administration process that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire HGT Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the study procedure. The Investigator will promptly supply all information identified and requested by the Sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device, or procedure.

The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted] United Kingdom OR
United States FAX: [redacted]
Email: [redacted]

AND

Shire HGT Medical Monitor:
FAX: [redacted] (United States)

The Investigator may also call the Medical Monitor directly (optional):

Shire HGT Medical Monitor: [redacted] MD
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted] (24 hour access)
Email: [redacted]

AND

Clinical Project Manager CC'd: [redacted]

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

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

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

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication

7.23.5.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. The relationship of each AE to study medication must be recorded. In addition AEs may be considered to be related to the IDDD, the IDDD surgical procedure, or the IT administration process. Since the AE may be deemed to be related to more than one of these factors, as many of these IDDD-related options as apply should be indicated on the eCRF.

7.23.5.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The Investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire HGT Medical Monitor (see Section 7.23.5.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The Investigator or other physician in attendance in such an emergency must contact the Shire HGT Medical Monitor as soon as possible.

The Investigator, along with the Shire HGT Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.24 Abuse, Overdose and Medication Errors

Abuse, misuse, overdose or medication error must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.23.

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed **by the protocol)**
- **Overdose –** Overdosage with adverse clinical consequences is not anticipated with the use of HGT-1410. Additionally, HGT-1410 will be given in a clinical setting by a health care provider.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

7.25 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered by the sponsor to be possibly, probably, or definitely related to study drug **or the IDDD**, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered by the sponsor to be possibly, probably, or definitely related to the study drug **or the IDDD**, then the site will be instructed to halt further HGT-1410 administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.26 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of HGT-1410 throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of HGT-1410. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a pregnancy test is positive the patient will be discontinued from the study, and the Investigator must contact the Shire HGT Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.27 Removal of Patients from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.

- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.28 Other Study Procedures

This section is not applicable.

7.29 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last HGT-1410 administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of HGT-1410 in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal HGT-1410 dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
- ABR
- MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments performed prior to the administration of anesthesia)
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments

Patients will receive HGT-1410 IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs
- Hematology
- Serum chemistry
- Urinalysis
- Pregnancy testing (applicable females only)
- Neurological examination (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal HGT-1410 treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, AND 54

- Head circumference
- Visual and hearing assessments
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and /or serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR
- MRI of the head
- Full neurodevelopmental testing, including VABS-II (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QoL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of HGT-1410

Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

- Physical examination
- ECG (performed following IT study drug injection)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- HGT-1410 IT injection (Day 2 ±2 days)
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

8.3 End of Study/Early Termination Procedures: Month 55

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of HGT-1410.

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, expanded access, commercially available).

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Urine heparan sulfate and heparan sulfate derivatives
- Plasma and serum heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing
- ABR (unless performed at Month 54)
- MRI of the head (unless performed at Month 54)
- CSF sample collection (unless performed at Month 54)
- Neurological examination
- Full neurodevelopmental testing, including VABS-II
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QoL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments
- X-ray of device, if the patient is to continue to receive intrathecal HGT-1410 beyond the end of the study

All patients who discontinue the study early will have their IDDD removed.

Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 56

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire HGT or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of HGT-1410 in patients with MPS IIIA. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables, and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

No a priori hypotheses will be tested. Exploratory hypotheses may emerge from the data analysis, in which case, appropriate testing methods will be applied and specified in the statistical analysis plan.

There are no formal hypotheses associated with the evaluation of the safety and performance of the IDDD device (SOPH-A-PORT Mini S). All analyses of device safety and performance will be descriptive and no statistical testing will be performed. Device related analyses will be based on patients for whom the device implant procedure was performed and are described in the sections below.

10.2 Determination of Sample Size

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

10.3 Analysis Populations

The primary analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. This population will be used to perform both safety and efficacy analyses. The collection of detailed data pertaining to the SOPH-A-PORT mini S will permit device-related analyses to be conducted in the subset of patients in the primary analysis population who had the SOPH-A-PORT Mini S implant procedure performed**.**

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of AEs, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients who had an IDDD surgical procedure and/or received administration of HGT-1410 will be included in the safety analysis.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each dose group, the number and percentage of patients having any AE, having an AE in system organ class, and having each individual AE. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events , defined as all AEs from the time of the surgery for IDDD implantation to the last follow up contact, ie, 30 days after the last HGT-1410 administration, (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication/procedure.

Treatment-emergent AEs deemed related to HGT-1410 administration will be summarized separately.

IDDD, and procedure-related AEs will be summarized within system organ class by preferred term. IDDD and procedure-related AEs will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure (including post-implant infections) and IT administration process. These summaries will be presented by device and overall, as appropriate.

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis and CSF) results will be presented in summary tables by evaluation visit. Changes from baseline will be summarized for each post-baseline visit. Each laboratory result will be categorized as a patient having had (1) an Abnormal and Clinically Significant (CS) value at any time, (2) no CS values at any time but had at least one Abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any time 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.

The observed values and changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

The observed values and changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by number and percentage of positive and negative specimens by evaluation visit, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.2 Other Observations Related to Safety

10.6.2.1 IDDD Performance

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

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

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

10.6.3 Secondary Analysis

10.6.3.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of HGT-1410 administration on QoL measures will be examined by presenting mean change from baseline by dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.3.2 Pharmacodynamic Analyses

To determine the effects of HGT-1410 administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparan sulfate reduction (in CSF and urine) will be examined using mean change and the corresponding 95% confidence interval. The concentration of inflammatory cytokines in serum and CSF will also be examined. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

The planned analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the Investigators must provide the Sponsor with a completed Form Food and Drug Administration (FDA) 1572 or Investigator Agreement. Study medications may be administered only under the supervision of the Investigators listed on this form. Curriculum vitae must be provided for the Investigators and sub-investigators listed on Form FDA 1572 or Investigator Agreement.

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

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

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

Before Shire HGT initiates the trial (ie, obtains informed consent [assent if applicable] from the first patient), it is the responsibility of the Investigator to ensure that the following documents are available to Shire HGT or their designee:

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire HGT. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire HGT.

11.8 Device Failure Adjudication Process

The final cause for device failures will be adjudicated by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire HGT and the Investigators. In addition, a decision on the part of Shire HGT to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.7.6).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

12 LIST OF REFERENCES

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Appendix 1 Schedule of Events

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**
Informed Consent/Enrollment		●				
Physical Examination	●	●	●		●	
Height and Weight	●	●			●	
Head Circumference	●			●	●	
Visual and Hearing Assessment				●	●	
ECG	●		●[b]		●	
Vital Signs	●	●	●		●	
Hematology	●	●			●	
Serum Chemistry	●	●			●	
Pregnancy Testing[n]	●	●				
Urinalysis	●	●			●	
Leukocyte pellet preparation[o]	●					
Urine Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Plasma and serum Heparan Sulfate and Heparan Sulfate Derivatives	●			●[e]	●	
Anti-rhHNS antibody testing (serum and CSF)[l]	●			●	●	
Auditory Brainstem Response (ABR)	●			●	●[p]	
MRI of the Head	●			●	●[p]	
CSF Sample Collection[m]	●		●[c]		●[c, p]	
HGT-1410 dosing: every 28 (±7) days [d, g,]			●			
Neurological Examination[h]	●	●	●		●	
Full Neurodevelopmental Testing[i]	●			●	●	
Children's Sleep Habits Rating Scale	●			●	●	

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**
Child Health Questionnaire-50	●			●	●	
Child Health Questionnaire-87	●			●	●	
Infant Toddler QOL Questionnaire	●			●	●	
Concomitant Medications, Therapies, and Procedures	●	●	●		●	●
Adverse Event Monitoring	●	●	●		●	●
X-ray examination of device (if treatment is to continue beyond end of study)					●	
Removal of IDDD				●[q]	●[q]	

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; EOS = end of study ; ECG = electrocardiogram; IT = intrathecal; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as presented here at Month 54, corresponds to Month 48 in HGT-SAN-067, but represents a total of 54 months of study treatment (48 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug.

[c] CSF samples will be obtained according to the process with in the study operations manual). An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of HGT-1410 and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or a LP may be performed (can occur up to 5 times in a 6 month period).

[d] Patients may be discharged as early as 4 hours post HGT-1410 infusion (ie, on Day 2) when deemed clinically stable by the Investigator.

[e] Specimens collected once a month, at Day 1 of the first treatment week.

[f] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] The neurological exam should not occur sooner than 4 hours after administration of study drug or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

[i] Full neurodevelopmental testing includes an assessment with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

[j] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[k] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled HGT-1410 IT dose.

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[k] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, and 54 (from the start of HGT-SAN-055)**	**EOS[f] Month 55 (from the start of HGT-SAN-055)**	**Month 56 Safety Follow-up[j]**

[l] Blood sample drawn before IT injection of HGT-1410.

[m] CSF will be tested for standard chemistries, heparan sulfate and heparan sulfate derivatives, anti-rhHNS antibodies, and MPS exploratory biomarkers.

[n] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[o] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

[P] These assessments are not to be performed at an EOS visit conducted at Month 55 if they were performed at the Month 54 visit

[q] The IDDD will be removed at the Month 54 visit, or at the EOS visit if the patient discontinues the study prior to the Month 54 visit

Appendix 2 Neurodevelopmental and Behavioral Assessments

Table A2-1 and Table A2-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table A2-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table A2-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child’s abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III) [23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II) [24]

Purpose:

The KABC-II measures a child’s cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery’s results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS) [5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Expected Adverse Device Effects

Procedure-Related Complications

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

Intrathecal Access Complications

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

System-Related Complications

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

Appendix 4 Protocol Amendment 5 Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol HGT-SAN-067 has been amended to remove the requirement for patients to have a WBC greater than 100 cubic millimeters in CSF just prior to dosing. It is believed that sufficient experience with HGT-1410 now exists that it is safe to proceed with dosing without waiting for CSF clinical laboratory results. This also reduces the time that a needle is in the device port, thus reducing the risk of introducing infection.

Previous Amendment: Amendment 4; 3 May 2013

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: Remove the pre-dose CSF requirement of WBC >100 cc
Section impacted by this change: Section 8.2
CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection. ~~Note: Patients will not receive study drug if the pre-dose CSF contains >100 WBC per cubic millimeter.~~
Other sections impacted by this change: None

Change: Minor editorial clarification
Section impacted by this change: Section 6.3.1
CSF samples will be obtained prior to each injection for **clinical laboratory** ~~safety~~ evaluation and **potential** biomarker studies.
Other sections impacted by this change: None

Appendix 5 Protocol Signature Page

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 Amendment 5

Final Date: 21 June 2010

Amendment 1 Date: 22 January 2011

Amendment 2 Date: 13 January 2012

Amendment 3 Date: 28 August 2012

Amendment 4 Date: 3 May 2013

Amendment 5 Date: 17 January 2014

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

Signatory:

Investigator

_____

Signature **Date**

_____

Printed Name

I have read and approve the protocol described above.

Signatory:

Shire HGT Medical Monitor

[redacted]

Signature **Date**

[redacted], MD

Printed Name

Appendix 6 The National Cancer Institute Common Terminology Criteria version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
Device Names:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire and PORT-A-CATH® II Low Profile™ *Intrathecal Implantable Access System* (Smiths device)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421, United States [redacted]
Medical Monitor:	[redacted] MD, PhD [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012
Amendment 3:	28 August 2012
Amendment 4:	3 May 2013
Amendment 5:	17 January 2014
Amendment 6:	10 July 2014

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421, United States

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)

Name of Active Ingredient:

rhHNS, HGT-1410

Name of Inactive Ingredient:

N/A

Names of Devices:

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

and

PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

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

Study Phase: I/II

Device, Intended Use

The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1410 indicated for intrathecal delivery intermittently over a long period of time.

Prior to approval of Amendment 4, patients were implanted with a PORT-A-CATH (Smith's device). After approval of Amendment 4 all PORT-A-CATH IDDDs requiring revision or replacement will be replaced with a SOPH-A-PORT at a time judged appropriate by the Investigator.

Study Objectives:

Primary Objective:

The primary objective of this study is:

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

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

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

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

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life 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 and heparan sulfate derivatives in CSF and glycosaminoglycans (GAG), including heparan sulfate and heparan sulfate derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with 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. Initially, patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study. Following approval of protocol Amendment 4, patients in the 10 mg group will have their dose increased to 45 mg per month.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of HGT-1410 in

Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures and again at Month 54. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments in the HGT-SAN-055 study. These assessments will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out. A MRI of the head will be performed at Months 12, 24, 36, 54, 66 and 78 and ABR testing will be performed at Months 12, 24, and 36 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study). Note: X-rays may be performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy should be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055). Patients will also have X-ray examinations of the device performed at the EOS visit if the patient is to continue to receive intrathecal HGT-1410 beyond the end of the study.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria

will be applied and will be based on the types and severity of adverse events (AEs) reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 78). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child health questionnaires, and MRI.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month 79) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of HGT-1410. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the operations manual (for PORT-A-CATH) or the IDDD Manual (for SOPH-A-PORT), which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), HGT-1410 will be administered via lumbar puncture (LP).

If there are medical contra-indications to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive lumbar punctures may be performed across the studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD may be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.

Continued treatment via lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

If there is no significant safety risk in the opinion of the Investigator, a non-functional IDDD may be 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 will be introduced for those patients requiring

replacement or revision. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments are included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

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

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with HGT-1410.

Test Product; Dose; and Mode of Administration: Recombinant human heparan N-sulfatase (rhHNS, HGT-1410) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly). Patients assigned to the 10 mg monthly dose will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of the protocol amendment.

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
3. The patient has a known or suspected local or general infection
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
6. The patient has a functioning CSF shunt device

7. The patient has shown an intolerance to an implanted device

Duration of Treatment:

The study duration will be 6 years.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods: The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval (CI) around the mean will also be estimated and presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed Study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 6: 10 July 2014

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CNS	central nervous system
CO_2	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
CRIM	cross-reacting immunologic material
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture

Abbreviation	Definition
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
EU	European Union
FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonization
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	instructions for use
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MABC-2	Movement Assessment Battery for Children, Second Edition

Abbreviation	Definition
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
NCI	National Cancer Institute
NCS	not clinically significant
PE	pressure-equalization
QoL	quality of life
Q4W	once per month
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UADE	unanticipated adverse device effect
US	United States
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)

Abbreviation	Definition
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. Initially, the patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055. Following the analysis of data from HGT-SAN-055, patients in the lowest dose group will have their dose increased to 45 mg, as outlined in Section 1.3, below.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is LSD caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A (MPS IIIA) results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtype A the most common of these.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1-3] In summary, MPS IIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5 - 7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8]

A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11, 12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the HGT-1410 clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an intrathecal drug delivery device (IDDD) due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13, 14 - 16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L- Iduronidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358).

This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse event (AE) monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT-HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of HGT-1410 in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

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

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, HGT-1410 was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of HGT-1410 leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of HGT-1410 to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 µg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 µg dose given IT every other week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mgHGT-1410 given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, and the highest dose of HGT-1410 was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no HGT-1410-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin

relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene.

In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs, HGT-1410 (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of HGT-1410 into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg HGT-1410 resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis and astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg HGT-1410 per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of HGT-1410 (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg HGT-1410 was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 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 patients who completed Study HGT-SAN-055 and elected to continue therapy with HGT-1410.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the end of study (EOS) evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will initially receive HGT-1410 at the same dose and schedule as they received in Study HGT-SAN-055. Patients assigned to 10 mg monthly will have their dose

increased to 45 mg monthly once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4. Based on analyses performed at the completion of Study HGT-SAN-055 a decline in the primary pharmacodynamic parameter, CSF heparan sulfate, was observed. This response to therapy was exhibited at all dose levels, however, the greatest impact was at the 2 higher dose levels. An effect on CSF heparan sulfate demonstrated in vivo activity of HGT-1410 in the target anatomical compartment. This effect is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410. As no apparent difference in safety profile was observed between the 3 dose groups, it was believed that the increase in the potential therapeutic benefit of the higher dose outweighed any potential increase in risks for this lowest dose group.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of HGT-1410 and PORT-A-CATH IDDD and SOPH-A-PORT Mini S device.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients 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.

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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.

2.3 Exploratory Objective

An exploratory objective of this study is:

- [redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

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

- adverse events (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).

3.2 Secondary Endpoints

The secondary endpoints of this study are 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 and heparan sulfate derivatives in CSF and GAG, including heparan sulfate and heparan sulfate derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), (also known as Brainstem Auditory Evoked Potentials).

3.3 SOPH-A-PORT Mini S Assessments

[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of IT administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted HGT-1410 treatment. Patients will initially continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

- 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)

Patients assigned to Group 1 will initially receive 10 mg monthly but will have their dose increased to 45 mg monthly (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

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 patient received their first IT dose of HGT-1410 in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be

added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out.

A MRI of the head will be performed at Months 12, 24, 36, 54, 66 and 78 and ABR testing will be performed at Months 12, 24, 36 and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055). If patients are to continue to receive HGT-1410 using the IDDD beyond the duration of this study, they will also have X-ray examinations of the device performed at the EOS visit, to document correct positioning.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 eCRFs. Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 78). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child health questionnaires, and MRI. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit (ie, Month 79) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to administer HGT-1410. However, if a patient's PORT-A-CATH IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the PORT-A-CATH Instructions for Use (IFU), which describes the investigation and management of IDDD-related issues with this device. This will include possible partial revision or complete replacement of the PORT-A-CATH IDDD with a SOPH-A-PORT IDDD. For malfunctions involving the SOPH-A-PORT Mini S, site personnel will refer to the SOPH-A-PORT IFU. For either IDDD, a maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, HGT-1410 will be

administered via lumbar puncture (LP). If implantation of a replacement IDDD is not possible, investigational drug may be administered by LP for a maximum of 12 successive monthly doses. At that point, a safety discussion needs to take place between the investigator and the Sponsor to determine the risk/benefit of further dosing by LP.

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

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the Sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of HGT-1410 via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT HGT-1410 administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in the HGT-SAN-067 study.

In order to traverse the blood-brain barrier, Shire is evaluating HGT-1410 delivered directly to the CNS using an IDDD. The advantage of using an IDDD is that it obviates the need for multiple lumbar punctures for drug delivery. Drug products will be administered through this port or, if the IDDD is non functional, via lumbar puncture.

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

4.3 Study Duration and Dates

The study duration will be 6 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue HGT-1410 treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the Investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the Investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the Investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the Investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the Investigator
3. The patient has a known or suspected local or general infection
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
6. The patient has a functioning CSF shunt device
7. The patient has shown an intolerance to an implanted device

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Intrathecal Drug Delivery Device

The PORT-A-CATH will continue to be used for the administration of drug product for each patient until such time as an IDDD replacement may be required. Following implementation of protocol Amendment 4, any replacements will be performed using the SOPH-A-PORT Mini S.

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

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

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

Further details are provided in the Instructions for Use.

6.1.3 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

HGT-1410 for IT administration will be provided by Shire. HGT-1410 will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will initially receive the same dose of HGT-1410 they received 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)

Patients assigned to Group 1 will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

The study drug will be administered through an IDDD.

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

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

6.3 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT HGT-1410 dosing for safety assessments, designated Day 1, on each HGT-1410 treatment week, and if no safety concerns exist, will receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the Investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the Investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details).

6.3.1 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for clinical laboratory evaluation and potential biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling. Site personnel should refer to the operations manual for instructions on the use of topical anesthesia prior to accessing the IDDD reservoir.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the IDDD Manual and Section 6.3.2. Intrathecal Administration of HGT-1410

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive HGT-1410 via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 4 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

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

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

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.3.2). The investigation and management of a malfunctioning IDDD is detailed in the PORT-A-CATH or SOPH-A-PORT IFUs. Partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.3.2 Administration of HGT-1410 via Lumbar Puncture Guidance Concerning Performance of Lumbar Puncture for Study Drug Administration and Cerebrospinal Fluid Sample Collection

It is intended that the IDDD will be used to deliver all IT injections of study drug and to obtain CSF samples. If the IDDD appears to be nonfunctional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD manual (s), which provides details on the investigation and management of any IDDD-related issues. This may include possible partial revision or complete replacement of the IDDD as indicated. If the nonfunctional IDDD is a PORT-A-CATH device, then it will be replaced by a SOPH-A-PORT Mini S device.

If there are medical contra-indication to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive lumbar punctures may be performed across studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of

12 consecutive lumbar punctures, a new IDDD will be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.

Continued treatment via repeat lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases of patients where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

6.4 Method of Assigning Patients to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with HGT-1410. Patients will initially receive the same dose of HGT-1410 they received in Study HGT-SAN-055. Patients assigned to Group 1 (10 mg once per month [Q4W]) will have their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

6.5 Blinding

Not applicable; as this trial is not blinded.

6.6 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Dictionary (WHO-DD).

6.7 Restrictions

6.7.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the Investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.

- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than HGT-1410 or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.7.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.7.3 Patient Activity Restrictions

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

6.8 Treatment Compliance

HGT-1410 is administered under controlled conditions by the Investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.9 Packaging and Labeling

6.9.1 Drug Product

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of HGT-1410. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminium seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9.2 SOPH-A-PORT Mini S Access Port

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

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

6.10 Storage and Accountability

6.10.1 Investigational Product

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

All HGT-1410 study drug delivered to an Investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

6.10.2 Intrathecal Drug Delivery Device

6.10.2.1 PORT-A-CATH IDDD

Please refer to the operations manual for return instructions.

6.10.2.2 SOPH-A-PORT Mini S IDDD

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

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

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

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

6.11 Investigational Product Retention at Study Site

All HGT-1410 study drug delivered to an Investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the Sponsor or its designee or disposed of after Sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory Manual.

7.2 Physical Examination

A full physical examination or a symptom-directed physical examination of each patient will be performed at time points detailed in Appendix 1 Schedule of Events.

Any changes from the screening physical examination will be captured as AEs in the eCRF.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.9). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological
- Endocrine
- Genitourinary

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory Manual. The conduct of a clinical trial in an extremely rare disease such as MPS IIIA provides a unique opportunity to collect samples for potential biomarker research. In the context of this study, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of the MPS IIIA pathogenic process, or a pharmacologic response to experimental therapy with HGT-1410. In addition to exploration of potential biomarkers, as part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.7.4 Serum Anti-rhHNS Antibody and Sample Storage

Blood samples will be collected and evaluated at Shire or Shire-designated laboratories for the determination of anti-rhHNS antibodies.-Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory Manual.

7.7.5 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the Investigator).

7.7.5.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.7.5.2 Urine Glycosaminoglycans

A urine sample will be collected for the determination of GAG (including heparan sulfate and heparan sulfate derivatives) and the analysis will be performed at Shire, or Shire designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.6 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.6.1, 7.7.6.2, and 7.7.6.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or ribonucleic acid (RNA) may become used as they become available in the future.

7.7.6.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.6.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire designated laboratories.

7.7.6.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of anti-rhHNS antibodies at Shire or Shire designated laboratories.

7.7.6.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of MPS exploratory biomarkers at Shire or Shire-designated laboratories.

7.7.7 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory Manual to be provided by Shire.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the Investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the Investigator believes causes significant conductive hearing loss and impairment of daily living, the Investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Device Data

[redacted]

[redacted]

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. After full approval of protocol Amendment 4, all IDDD replacements will be made with the SOPH-A-PORT IDDD. If the IDDD device is a PORT-A-CATH IDDD, it will be replaced by a SOPH-A PORT IDDD. Management details for the PORT-A- CATH IDDD or for the SOPH-A PORT IDDD are provided in the respective device's IFU. Procedures for implantation are detailed in the relevant device's Instructions for Use Manual and in the training materials provided by Shire. The patient will be under general anesthesia for this procedure. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly, and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the IDDD Manual).

A post-operative check of the IDDD and incision will be performed on Day 4 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Device Related Study Procedures

7.13.1 IDDD Implantation or Revision Procedures

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

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

Details of the implantation/revision and malfunctions/failure for the SOPH-A-PORT will be documented on the patient's eCRF.

7.13.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative x-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, as needed, throughout the study. If the patient is to receive intrathecal HGT-1410 beyond the end of the study, an X-ray will be performed at the end of the study to verify that the IDDD is in the correct position. At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional x-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray may be performed to assess the potential cause of malfunction. Fluoroscopy may be used during device implant or revision procedures.

7.13.3 CSF Sampling Procedure

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

7.13.4 Device Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's IFU due to a device-related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

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

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

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

If the IT space is not accessible via the IDDD, study drug may be administered by LP up to 5 times.

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

7.14 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision

or replacement is done. Following implementation of Amendment 6 the CSF opening pressure measurement will not be required with the LP.

7.15 Dispensing Study Drug

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. HGT-1410 will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, HGT-1410 may be administered via LP. See Section 6.3.2 for details.

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

7.16 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.17 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

7.18 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.19 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.20 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.20.1, 7.20.2, and 7.20.3.

7.20.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age.

7.20.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being.

7.20.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.21 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.22 Adverse Events

7.22.1 Definitions of Adverse Events and Serious Adverse Events

7.22.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

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

Throughout the study, the Investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to study drug. The Investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All AEs should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of HGT-1410. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to HGT-1410 caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of HGT-1410 to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal HGT-1410 therapy to date.

7.22.1.2 Potential Adverse Events: Intrathecal recombinant human heparan N-sulfatase

ADVERSE EVENTS RELATED TO THE DIRECT DELIVERY OF HGT-1410 TO THE CNS THROUGH INTRATHECAL ADMINISTRATION

Examples of AEs observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory paresthesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time

ADVERSE EVENTS DUE TO SYSTEMIC EXPOSURE TO HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

7.22.1.3 IDDD-related Adverse Events

IDDD ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site, or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A malfunction of the device (defined in Section 7.22.2.2) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section7.22.2.3), the device may need to be replaced or repaired. Hospitalization for such a procedure will be reported as a serious adverse event (SAE). Details of the cause of IDDD malfunction or failure will be recorded on the Device Malfunction/Failure CRF. A list of the more common IDDD AEs is included in Appendix 3.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS

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

IT ADMINISTRATION PROCESS ADVERSE EVENTS

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

7.22.1.4 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization. Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s). *Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs."*

2. Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21CFR812.3[s] or other regulatory requirements, as applicable).

7.22.2 Device-Associated Definitions

7.22.2.1 Device Revision (Partial and Full)

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

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

7.22.2.2 Device Malfunction

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

7.22.2.3 Device Failure

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

7.22.3 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page. Adverse events are graded as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3 Adverse Event Severity

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

7.22.4 Relatedness of Adverse Events and Serious Adverse Events

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

Table 7-4 Adverse Event Relatedness

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

7.22.5 Procedures for Recording and Reporting Adverse Events

7.22.5.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE regardless of relationship to investigational product, device, device surgical procedure, or IT administration process that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the Investigator as to the relationship of the SAE to the investigational product and or device. The Investigator will promptly supply all information identified and requested by the Sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device, or procedure.

The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the Investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted] United Kingdom OR
United States FAX: [redacted]
Email: [redacted]
AND
Shire HGT Medical Monitor:
FAX: [redacted] (United States)

The Investigator may also call the Medical Monitor directly (optional):

Shire HGT Medical Monitor: [redacted], MD, PhD
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted] (24 hour access)
Email: [redacted]
AND
Clinical Project Manager CC'd: [redacted]

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

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

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

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the Sponsor will also notify the Investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication

7.22.5.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. The relationship of each AE to study medication must be recorded. In addition AEs may be considered to be related to the IDDD, the IDDD surgical procedure, or the IT administration process. Since the AE may be deemed to be related to more than one of these factors, as many of these IDDD-related options as apply should be indicated on the eCRF.

7.22.5.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the Investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The Investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware. In an emergency situation, the Investigator should contact the Shire Medical Monitor (see Section 7.22.5.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The Investigator or other physician in attendance in such an emergency must contact the Shire Medical Monitor as soon as possible.

The Investigator, along with the Shire Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.23 Abuse, Overdose and Medication Errors

Abuse, misuse, overdose or medication error must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.22.

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed **by the protocol)**
- **Overdose –** Overdosage with adverse clinical consequences is not anticipated with the use of HGT-1410. Additionally, HGT-1410 will be given in a clinical setting by a health care provider.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

7.24 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered by the sponsor to be possibly, probably, or definitely related to study drug **or the IDDD**, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered by the sponsor to be possibly, probably, or definitely related to the study drug **or the IDDD**, then the site will be instructed to halt further HGT-1410 administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.25 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of HGT-1410 throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of HGT-1410. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a pregnancy test is positive the patient will be discontinued from the study, and the Investigator must contact the Shire Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.26 Removal of Patients from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

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

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the Sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the Investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.

- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the Sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.27 Other Study Procedures

This section is not applicable.

7.28 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last HGT-1410 administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of HGT-1410 in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the Investigator. A decision about enrollment will be made following discussion with the Medical Monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal HGT-1410 dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine GAG, including heparan sulfate and heparan sulfate derivatives
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (serum and CSF)
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
- ABR
- MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments performed prior to the administration of anesthesia)
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments

Patients will receive HGT-1410 IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the Investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs
- Hematology (after Month 54 frequency reduced to Q3 Months)
- Serum chemistry (after Month 54 frequency reduced to Q3 Months)
- Urinalysis (after Month 54 frequency reduced to Q3 Months)
- Pregnancy testing (applicable females only)
- Neurological examination (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal HGT-1410 treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, 54, 66, AND 78

- Head circumference
- Visual and hearing assessments
- Urine GAG, including heparan sulfate and heparan sulfate derivatives (also performed at Month 60 and Month 72, ie, Q6 Months following Month 54)
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (also performed at Month 60 and Month 72, ie, Q6 Months following Month 54)
- ABR (not performed after Month 54, ie not on Month 66 or 78)
- MRI of the head
- Full neurodevelopmental testing, including VABS-II (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QoL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of HGT-1410

Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the Investigator.

- Physical examination (after Month 54 the full physical examination will be performed at Months 54, 66, and 78. The remainder of the physical examinations will be symptom-directed)
- ECG (performed following IT study drug injection)(after Month 54 performed Q3 months)
- Vital signs
- CSF sample collection (obtained prior to IT study drug injection)
- HGT-1410 IT injection (Day 2 ±2 days)
- Neurological examination
- Concomitant medications, therapies, and procedures
- AE assessments

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

8.3 End of Study/Early Termination Procedures: Month 79

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of HGT-1410.

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, expanded access, commercially available).

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Urine GAG, including heparan sulfate and heparan sulfate derivatives
- Anti-rhHNS antibody testing (serum and CSF)
- MRI of the head (unless performed at Month 78)
- CSF sample collection (unless performed at Month 78)
- Neurological examination
- Full neurodevelopmental testing, including VABS-II
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- Infant toddler QoL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

All patients who discontinue the study early will have their IDDD removed.

Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 80

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of HGT-1410 in patients with MPS IIIA. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables, and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

No a priori hypotheses will be tested. Exploratory hypotheses may emerge from the data analysis, in which case, appropriate testing methods will be applied and specified in the statistical analysis plan.

There are no formal hypotheses associated with the evaluation of the safety and performance of the IDDD device (SOPH-A-PORT Mini S). All analyses of device safety and performance will be descriptive and no statistical testing will be performed. Device related analyses will be based on patients for whom the device implant procedure was performed and are described in the sections below.

10.2 Determination of Sample Size

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

10.3 Analysis Populations

The primary analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. This population will be used to perform both safety and efficacy analyses. The collection of detailed data pertaining to the SOPH-A-PORT mini S will permit device-related analyses to be conducted in the subset of patients in the primary analysis population who had the SOPH-A-PORT Mini S implant procedure performed**.**

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of AEs, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients who had an IDDD surgical procedure and/or received administration of HGT-1410 will be included in the safety analysis.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each dose group, the number and percentage of patients having any AE, having an AE in system organ class, and having each individual AE. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events , defined as all AEs from the time of the surgery for IDDD implantation to the last follow up contact, ie, 30 days after the last HGT-1410 administration, (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication/procedure.

Treatment-emergent AEs deemed related to HGT-1410 administration will be summarized separately.

IDDD and procedure-related AEs will be summarized within system organ class by preferred term. IDDD and procedure-related AEs will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure (including post-implant infections) and IT administration process. These summaries will be presented by device and overall, as appropriate.

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis and CSF) results will be presented in summary tables by evaluation visit. Changes from baseline will be summarized for each post-baseline visit. Each laboratory result will be categorized as a patient having had (1) an Abnormal and Clinically Significant (CS) value at any time, (2) no CS values at any time but had at least one Abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any time 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.

The observed values and changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

The observed values and changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by number and percentage of positive and negative specimens by evaluation visit, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.2 Other Observations Related to Safety

10.6.2.1 IDDD Performance

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

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

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

10.6.3 Secondary Analysis

10.6.3.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of HGT-1410 administration on QoL measures will be examined by presenting mean change from baseline by dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.3.2 Pharmacodynamic Analyses

To determine the effects of HGT-1410 administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparan sulfate reduction (in CSF) will be examined using mean change and the corresponding 95% confidence interval. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

10.6.4 Interim Analysis

No formal analysis or interim statistical testing for early stopping of the trial is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting, or general planning purposes.

The planned final analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

The study will be monitored by the Sponsor or its designee. On site monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted

according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

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

- Curricula vitae of Investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of Investigator and sub investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire. All trial documents will be available in a Trial Master File (TMF) at the Investigator/trial site and at Shire.

11.8 Device Failure Review Process

The final cause for device failures will be reviewed by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

11.9 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the Sponsor or an Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire and the Investigators. In addition, a decision on the part of Shire to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence by the Investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.7.7).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the Investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the Sponsor with complete test results and all data developed in the study in a timely manner.

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

12 LIST OF REFERENCES

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Appendix 1 Schedule of Events

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Month 7 through Month 80 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)					
Assessment	**Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, 54, 60, 72 and 78 (from the start of HGT-SAN-055)**	**Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)**	**EOS[e] Month 79 (from the start of HGT-SAN-055)**	**Month 80 Safety Follow-up[f]**
Informed Consent/Enrollment		●		●[r]			
Physical Examination	●	●[p]	●[p]	●[p]			
Symptom-Directed Physical Examination		●[p]	●[p]			●	
Neurological Examination[h]	●	●	●			●	
Height and Weight	●	●				●	
Head Circumference	●			●		●	
Visual and Hearing Assessment				●		●	
ECG	●		●[b]				
Vital Signs	●	●	●			●	
Hematology	●	●				●	
Serum Chemistry	●	●				●	
anti-rhHNS antibody testing (serum)[k]	●			●		●	
Plasma storage for biomarkers	●	●		●		●	
Pregnancy Testing[l]	●	●				●	
Urinalysis	●	●				●	
Urine GAGS	●			●[e]		●	
Leukocyte pellet preparation[m]	●						
CSF chemistry and cell counts[c]	●	●				●	
CSF sample storage[c,o]	●	●				●	
CSF Heparan Sulfate and Heparan Sulfate Derivatives[c]	●			●	●		
Anti-rhHNS antibody testing (CSF)[c]	●			●		●	

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Month 7 through Month 80 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)					
Assessment	**Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, 54, 60, 72 and 78 (from the start of HGT-SAN-055)**	**Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)**	**EOS[e] Month 79 (from the start of HGT-SAN-055)**	**Month 80 Safety Follow-up[f]**
Auditory Brainstem Response (ABR)[q]	●			●			
MRI of the Head	●			●		●[n]	
HGT-1410 dosing: every 28 (±7) days [d, g,]			●				
Full Neurodevelopmental Testing[i]	●			●		●	
Children's Sleep Habits Rating Scale	●			●		●	
Child Health Questionnaire-50	●			●		●	
Child Health Questionnaire-87	●			●		●	
Infant Toddler QOL Questionnaire	●			●		●	
Concomitant Medications, Therapies, and Procedures	●	●	●			●	●
Adverse Event Monitoring	●	●	●			●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; EOS = end of study ; ECG = electrocardiogram; IT = intrathecal; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as-presented here at Month 78, corresponds to Month 72 in HGT-SAN-067, but represents a total of 78 months of study treatment (72 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug, after Month 54 it is to be performed every 3 months.

[c] CSF samples will be obtained according to the process with in the study laboratory manual. An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of HGT-1410 and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or a LP may be performed.

[d] Patients may be discharged as early as 4 hours post HGT-1410 infusion (ie, on Day 2) when deemed clinically stable by the Investigator.

[e] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

		Month 7 through Month 80 (from the start of HGT-SAN-055)				
		Dosed every 28 (±7) days (ie, Q4W)				
Assessment	**Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)**	**Pre-Tx Day 1[a]**	**IT dosing Day 2 (±2)**	**Months 12, 24, 36, 54, 60, 72 and 78 (from the start of HGT-SAN-055)**	**Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)**	**EOS[e] Month 79 (from the start of HGT-SAN-055)**	**Month 80 Safety Follow-up[f]**

[f] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] The neurological exam should not occur sooner than 4 hours after administration of study drug or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

[i] Full neurodevelopmental testing includes an assessment with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)

[j] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled HGT-1410 IT dose.

[k] Blood sample drawn before IT injection of HGT-1410.

[l] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[m] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

[n] These assessments are not to be performed at an EOS visit conducted at Month 79 if they were performed at the Month 78 visit

[o] CSF samples will be tested for MPS exploratory biomarkers, and possibly extractables and leachables.

[p] After Month 54 the Symptom-Directed PE is to be done monthly. Full PE is done monthly to Month 54 and then at least yearly, or more frequently at the investigator's discretion.

[q] ABR will not be performed after Month 54

[r] Informed consent will be obtained at Screening and Month 54

Appendix 2 Neurodevelopmental and Behavioural Assessments

Tables A2-1 and A2-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table A2-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table A2-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child’s abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III) [23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II) [24]

Purpose:

The KABC-II measures a child’s cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery’s results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II) [26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS) [5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Expected Adverse Device Effects

Procedure-Related Complications

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

Intrathecal Access Complications

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

System-Related Complications

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

Appendix 4 Protocol Amendment 6 Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol HGT-SAN-067 has been amended to extend the study and provide treatment with HGT-1410 for an additional 24 months (to Month 79 from start of study HGT-SAN-055); the frequency of hematology, serum chemistry and urinalysis assessments and the frequency of the ECG were reduced to Q3 months and the frequency of urine and plasma heparan sulfate and anti-rhHNS assessments was changed to Q6 months within this extended period. [redacted] replaced [redacted] in the role of Medical Monitor. The potential for determination of the levels of leachables from the IDDD in the CSF was added to the protocol. Other clarifications related to the IDDD use were added. Language clarifying that no formal interim analysis or interim statistical testing for early stopping is planned was added.

Previous Amendment: Amendment 5; 17 January 2014

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: Replacement of [redacted] by [redacted] as Medical Monitor
Section impacted by this change: Title page
Other sections impacted by this change: Synopsis, Section 7.22.5.1, Appendix 5 Signature Page

Change: Removal of the concentration of inflammatory cytokines in serum and CSF as a secondary endpoint
Section impacted by this change: Section 3.2
• ~~**Concentration of inflammatory cytokines in serum and CSF.**~~
Other sections impacted by this change: Synopsis, Section 10.6.3.2

Change: Addition of MRI of the head at Months 66 and 78 and deletion of ABR testing at Month 54
Section impacted by this change: Section 4.1
A MRI of the head will be performed at Months 12, 24, 36, 54, **66 and 78** and **ABR testing will be performed at Months 12, 24, and 36** ~~and 54~~ (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).
Other sections impacted by this change: Synopsis; Appendix 1 Table A1-1 Schedule of Events

Change: Last planned administration of HGT-1410 designated as Month 78 and EOS study procedures designated as Month 79
Section impacted by this change: Section 4.1
All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month ~~55~~ **78**). All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month ~~56~~ **79**) to collect updated information on AEs and concomitant medications, therapies, and procedures.
Other sections impacted by this change: Synopsis; Section 8.3, Appendix 1 Table A1-1 Schedule of Events

Change: Elimination of ABR after Month 36 and elimination of the x-ray of the device at end of study
Section impacted by this change: Section 4.1
The EOS procedures will include 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, and MRI ~~and an X-ray examination of the device.~~
Other sections impacted by this change: Synopsis, Appendix 1 Table A1-1 Schedule of Events

Change: Removal of limitation of number lumbar punctures to 5 and replaced with language that limits to 12 LP and consultation with Sponsor if more needed
Section impacted by this change: Section 4.1
~~Study drug may be administered via LP for a maximum of 5 successive monthly doses, after which, IDDD re-implantation or revision must occur.~~ **If there are medical contra-indications to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive lumbar punctures may be performed across the studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD may be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.** **Continued treatment via lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases where this treatment is**

very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.
Other sections impacted by this change: Synopsis; Section 6.3; Section 6.3.1, Section 6.3.3

Change: Study duration changed from 4 years to 6 years
Section impacted by this change: Section 4.3
The study duration will be 4 ~~-~~ **6** years.
Other sections impacted by this change: Synopsis; Appendix 1 Table A1-1 Schedule of Events

Change: Changes from screening physical exam to be added as AEs. Symptom-directed physical exam added.
Section impacted by this change: Section 7.2
A **full** physical examination or **a symptom-directed physical examination** of each patient will be performed **at time points** detailed in Appendix 1 Schedule of Events. **Any changes from the screening physical examination will be captured as AEs in the eCRF.**
Other sections impacted by this change: Synopsis; Appendix 1 Table A1-1 Schedule of Events

Change: Statement that it may be necessary to determine the levels of leachables from the device into the CSF and blood
Section impacted by this change: Section 7.7
The conduct of a clinical trial in an extremely rare disease such as MPS IIIA provides a unique opportunity to collect samples for potential biomarker research. In the context of this study, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of the MPS IIIA pathogenic process, or a pharmacologic response to experimental therapy with HGT-1410. In addition to exploration of potential biomarkers, as part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood.
Other sections impacted by this change: Appendix 1 Table A1-1 Schedule of Events footnotes

Change: Addition of urine glycosaminoglycans and serum anti-rhHNS antibody assessments at Month 60 and 72 (Q6 Months after Month 54) and clarification that urine

assessments include all glycosaminoglycans and not only heparan sulfate and its derivatives. Removal of plasma or serum assessments of heparan sulfate and its derivatives
Section impacted by this change: Section 7.7.4
• Urine **GAG, including** heparan sulfate and heparan sulfate derivatives **(also performed at Month 60 and Month 72, ie, Q6 Months following Month 54)** • ~~Plasma and /or serum heparan sulfate and heparan sulfate derivatives~~ • Anti-rhHNS antibody testing **(also performed at Month 60 and Month 72, ie, Q6 Months following Month 54)**
Other sections impacted by this change: Sections 7.7.5.2; 8.1, 8.2.1.1, 8.3, Appendix 1 Table A1-1 Schedule of Events

Change: Statement that catheters other than the Phoenix Neuro Disposable that are compatible with the device may be used.
Section impacted by this change: Section 7.13.1
Other catheter passers that are compatible with the SOPH-A-PORT Mini S may be used.
Other sections impacted by this change: None

Change: Statement that fluoroscopy will be used during all device implantation procedures during x-ray verification.
Section impacted by this change: Section 7.13.3
Fluoroscopy will be used during all device implantation procedures.
Other sections impacted by this change: None

Change: Elimination of measurement of CSF opening pressure at the time of an IDDD revision or replacement or lumbar puncture
Section impacted by this change: Section 7.14
A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision or replacement is done. **Following implementation of Amendment 6 the CSF opening pressure measurement will not be required with the LP.** .
Other sections impacted by this change: Sections 6.3.1, 7.12,

Change: Clarification of when a malfunction of the device should be reported as an AE
Section impacted by this change: Section 7.22.1.3
A malfunction of the device (defined in Section 7.23.2.1) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section 7.23.2.2), the device may need to be replaced or repaired. Hospitalization for such a procedure will be reported as a SAE. Details of the cause of IDDD malfunction or failure will be recorded on the Device Malfunction/Failure CRF. A list of the more common IDDD AEs is included in Appendix 3. ~~If the patient is admitted to the hospital in association with an IDDD event (eg for subsequent revision or replacement) the surgery will be recorded as a SAE.~~ **DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS** Examples of AEs related to **device** surgical procedures include, but are not limited to, the following: **events that occur during or following** IDDD implant/explant, IDDD adjustment, full revision, partial revision, IDDD removal, and delayed re-implantation after previous IDDD **removal (such as complications of anesthesia, excessive bleeding, wound hematoma) and post operative complications (such as post-operative infection).**
Other sections impacted by this change: none

Change: Additional SAE language
Section impacted by this change: Section 7.22.5.1
The Investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours
Other sections impacted by this change: None

Change: Change in frequency of hematology, serum chemistry and urinalysis assessments from monthly to every third month.
Section impacted by this change: Section 8.2.1.1
• Hematology **(after Month 54 frequency reduced to Q3 Months)** • Serum chemistry **(after Month 54 frequency reduced to Q3 Months)** • Urinalysis **(after Month 54 frequency reduced to Q3 Months)** • Pregnancy testing (applicable females only)
Other sections impacted by this change: Appendix 1 Table A1-1 Schedule of Events

Change: Frequency of ECG changed from Q4 weeks to Q3 Months
Section impacted by this change: Section 8.2.1.2
• ECG (performed following IT study drug injection)**(after Month 54 performed Q3 months)**
Other sections impacted by this change: Appendix 1 Table A1-1 Schedule of Events

Change: Indication that actions taken would not be captured for IDDD failures or malfunctions
Section impacted by this change: Section 10.6.2.1
The proportion of patients with at least one IDDD failure and/or malfunction, as well as the number of and reasons for IDDD failures/malfunctions **~~and actions taken~~** will be summarized. The proportion of patients for whom a successful first injection of study drug occurred will be reported among those for whom a first injection was attempted (i.e. those who had an apparently successful implantation and did not suffer a device removal or revision prior to first scheduled injection). The proportion of patients who had no failed injection attempts during the study will also be summarized. The corresponding 95% confidence intervals of the proportion of interest will be estimated, where appropriate. Injections not given for patient reasons (e.g. patient uncooperative, competing medical issue, etc) will not be included in the determination of these success proportions. ~~The frequency and reasons for unsuccessful injection attempts will be reported.~~
Other sections impacted by this change: None

Change: Addition of language to clarify that interim analyses were not intended to provide data for early stopping of the trial
Section impacted by this change: Section 10.6.4
12.1.2 Interim Analysis **No formal analysis or interim statistical testing for early stopping of the trial is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting, or general planning purposes.**
Other sections impacted by this change: None

Change: Clarification that device failures will be reviewed by a Shire team
Section impacted by this change: Section 11.8

The final cause for device failures will be **reviewed** ~~adjudicated~~ by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.
Other sections impacted by this change: None

Change: Addition of informed consent at Month 54
Section impacted by this change: Appendix 1 Table A1-1 Schedule of Events
Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures and again at Month 54.
Other sections impacted by this change: Appendix 1 Table A1-1 Schedule of Events, Synopsis

Appendix 5 Protocol Signature Page

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 Amendment 6
Final Date:	21 June 2010
Amendment 1 Date:	22 January 2011
Amendment 2 Date:	13 January 2012
Amendment 3 Date:	28 August 2012
Amendment 4 Date:	3 May 2013
Amendment 5 Date:	17 January 2014
Amendment 6 Date:	10 July 2014

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

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

[redacted] MD, PhD
Printed Name

Appendix 6 The National Cancer Institute Common Terminology Criteria version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*: – Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*: – Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.						
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY

Adverse Event	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
Device Names:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire and PORT-A-CATH® II Low Profile™ *Intrathecal Implantable Access System* (Smiths device)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421, United States
Medical Monitor:	[redacted] DO, [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012
Amendment 3:	28 August 2012
Amendment 4:	3 May 2013
Amendment 5:	17 January 2014
Amendment 6:	10 July 2014
Amendment 7:	08 February 2016

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421, United States

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)

Name of Active Ingredient:

rhHNS, HGT-1410

Name of Inactive Ingredient:

N/A

Names of Devices:

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

and

PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

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

Study Phase: I/II

Device, Intended Use

The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1410 indicated for intrathecal delivery intermittently over a long period of time.

Prior to approval of Amendment 4, patients were implanted with a PORT-A-CATH (Smith's device). After approval of Amendment 4 all PORT-A-CATH IDDDs requiring revision or replacement will be replaced with a SOPH-A-PORT at a time judged appropriate by the investigator.

Study Objectives:

Primary Objective:

The primary objective of this study is:

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

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

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

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

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life 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 and heparan sulfate derivatives in CSF and glycosaminoglycans (GAG), including heparan sulfate and heparan sulfate derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with 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. Initially, patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study. Following approval of protocol Amendment 4, patients in the 10 mg group had their dose increased to 45 mg per month.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of HGT-1410 in

Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the investigator.

All patients will have received a series of standardized neurodevelopment assessments in the HGT-SAN-055 study. These assessments will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out. An MRI of the head will be performed at Months 12, 24, 36, 54, 60, 72, 84, 96, and 102 and ABR testing will be performed at Months 12, 24, and 36 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study). Note: X-rays may be performed to investigate device malfunction, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy should be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055). Patients will also have X-ray examinations of the device performed at the EOS visit if the patient is to continue to receive intrathecal HGT-1410 beyond the end of the study.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria

will be applied and will be based on the types and severity of adverse events (AEs) reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 102). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child health questionnaires, and MRI.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month 103) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of HGT-1410. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the operations manual (for PORT-A-CATH) or the IDDD Manual (for SOPH-A-PORT), which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), HGT-1410 will be administered via lumbar puncture (LP).

If there are medical contra-indications to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive lumbar punctures may be performed across the studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD may be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.

Continued treatment via lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

If there is no significant safety risk in the opinion of the investigator, a non-functional IDDD may be 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 will be introduced for those patients requiring

replacement or revision. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments are included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

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

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with HGT-1410.

Test Product; Dose; and Mode of Administration: Recombinant human heparan N-sulfatase (rhHNS, HGT-1410) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly). Patients assigned to the 10 mg monthly dose had their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410.

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the investigator
3. The patient has a known or suspected local or general infection
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
6. The patient has a functioning CSF shunt device

7. The patient has shown an intolerance to an implanted device

Duration of Treatment:

The study duration allows patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in Study HGT-SAN-067 to receive treatment with HGT-1410 up to 8 years.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods: The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval (CI) around the mean will also be estimated and presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed Study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 7: 08 February 2016

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CNS	central nervous system
CO_2	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
CRIM	cross-reacting immunologic material
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture

Abbreviation	Definition
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
EU	European Union
FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonization
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	instructions for use
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MABC-2	Movement Assessment Battery for Children, Second Edition

Abbreviation	Definition
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
NCI	National Cancer Institute
NCS	not clinically significant
PE	pressure-equalization
QoL	quality of life
Q4W	once per month
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UADE	unanticipated adverse device effect
US	United States
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. Initially, the patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055. Following the analysis of data from HGT-SAN-055, patients in the lowest dose group had their dose increased to 45 mg, as outlined in Section 1.3, below.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is LSD caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A (MPS IIIA) results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtype A the most common of these.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1-3] In summary, MPS IIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5-7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8]

A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11, 12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the HGT-1410 clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an intrathecal drug delivery device (IDDD) due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13, 14-16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L- Iduronidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358).

This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse event (AE) monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT-HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of HGT-1410 in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

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

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, HGT-1410 was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of HGT-1410 leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of HGT-1410 to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 µg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 µg dose given IT every other week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mgHGT-1410 given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, and the highest dose of HGT-1410 was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no HGT-1410-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin

relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene.

In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs, HGT-1410 (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of HGT-1410 into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg HGT-1410 resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis and astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg HGT-1410 per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of HGT-1410 (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg HGT-1410 was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 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 patients who completed Study HGT-SAN-055 and elected to continue therapy with HGT-1410.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the end of study (EOS) evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will initially receive HGT-1410 at the same dose and schedule as they received in Study HGT-SAN-055. Patients assigned to 10 mg monthly had their dose

increased to 45 mg monthly once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4. Based on analyses performed at the completion of Study HGT-SAN-055 a decline in the primary pharmacodynamic parameter, CSF heparan sulfate, was observed. This response to therapy was exhibited at all dose levels, however, the greatest impact was at the 2 higher dose levels. An effect on CSF heparan sulfate demonstrated in vivo activity of HGT-1410 in the target anatomical compartment. This effect is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410. As no apparent difference in safety profile was observed between the 3 dose groups, it was believed that the increase in the potential therapeutic benefit of the higher dose outweighed any potential increase in risks for this lowest dose group.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of HGT-1410 and PORT-A-CATH IDDD and SOPH-A-PORT Mini S device.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients 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.

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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.

2.3 Exploratory Objective

An exploratory objective of this study is:

- [redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

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

- adverse events (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).

3.2 Secondary Endpoints

The secondary endpoints of this study are 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 and heparan sulfate derivatives in CSF and GAG, including heparan sulfate and heparan sulfate derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), (also known as Brainstem Auditory Evoked Potentials).

3.3 SOPH-A-PORT Mini S Assessments

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of IT administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted HGT-1410 treatment. Patients will initially continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

- 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)

Patients assigned to Group 1 will initially receive 10 mg monthly but had their dose increased to 45 mg monthly (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

Primarily main sites will be utilized; however, the sponsor and investigator will consider the feasibility of transitioning the patient's IT dosing to local sites to reduce the burden imposed by travel. At Month 18 (12 months after study start), patients that already received IT dosing at the main site may be eligible to transfer to a local site if in the opinion of the investigator there are no safety or medical concerns precluding this transition. Subsequent IT injections of HGT-4110 may be performed at either the main site or the local site. The local sites will be selected and approved by the sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: the main site may serve as a local site as needed; and in this case, the main site will follow the assessments scheduled for a local site). The qualification requirements for physicians at local sites will be identical to those for the main sites. Local sites will be trained if inexperienced with IT administration via an IDDD. Patients will be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the investigator. Dosing by IT injection may take place at the main site, rather than local site, if scheduled study assessments include MRI and cognitive assessments. Patients must review and agree to written informed consent/assent from the local site to participate in study procedures to be conducted at the local site prior to the conduct of these procedures.

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 patient received their first IT dose of HGT-1410 in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from

Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067 with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out.

An MRI of the head will be performed at Months 12, 24, 36, 54, 60, 72, 84, 96, and 102 and ABR testing will be performed at Months 12, 24, 36 and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study).

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055). If patients are to continue to receive HGT-1410 using the IDDD beyond the duration of this study, they will also have X-ray examinations of the device performed at the EOS visit, to document correct positioning.

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 eCRFs. Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month 102). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child health questionnaires, and

MRI. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit (ie, Month 103) to collect updated information on AEs and concomitant medications, therapies, and procedures.

It is anticipated that the IDDD will be used to obtain CSF samples and to administer HGT-1410. However, if a patient's PORT-A-CATH IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the PORT-A-CATH Instructions for Use (IFU), which describes the investigation and management of IDDD-related issues with this device. This will include possible partial revision or complete replacement of the PORT-A-CATH IDDD with a SOPH-A-PORT IDDD. For malfunctions involving the SOPH-A-PORT Mini S, site personnel will refer to the SOPH-A-PORT IFU. For either IDDD, a maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, HGT-1410 will be administered via lumbar puncture (LP). If implantation of a replacement IDDD is not possible, investigational drug may be administered by LP for a maximum of 12 successive monthly doses. At that point, a safety discussion needs to take place between the investigator and the sponsor to determine the risk/benefit of further dosing by LP.

If there is no significant safety risk in the opinion of the investigator, a non-functional IDDD may be left in situ for up to 3 months.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If a patient discontinues, or withdraws from the study, or the study is stopped by the sponsor, the IDDD will be removed as part of the EOS Procedures.

An overview of the study appears in the Schedule of Events (Appendix 1).

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of HGT-1410 via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT HGT-1410 administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in the HGT-SAN-067 study.

In order to traverse the blood-brain barrier, Shire is evaluating HGT-1410 delivered directly to the CNS using an IDDD. The advantage of using an IDDD is that it obviates the need for multiple lumbar punctures for drug delivery. Drug products will be administered through this port or, if the IDDD is non functional, via lumbar puncture.

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

SOPH-A-PORT Mini S revision, implantation or explantation will be performed at the main site. However, if in the opinion of the investigator, emergency removal is clinically necessary, device explantation may be performed at the patient's local site.

4.3 Study Duration and Dates

The study duration allows patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in Study HGT-SAN-067 to receive treatment with HGT-1410 up to 8 years.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue HGT-1410 treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the investigator
3. The patient has a known or suspected local or general infection
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation
6. The patient has a functioning CSF shunt device
7. The patient has shown an intolerance to an implanted device

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Intrathecal Drug Delivery Device

The PORT-A-CATH will continue to be used for the administration of drug product for each patient until such time as an IDDD replacement may be required. Following implementation of protocol Amendment 4, any replacements will be performed using the SOPH-A-PORT Mini S.

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

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

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

Further details are provided in the Instructions for Use.

6.1.3 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

HGT-1410 for IT administration will be provided by Shire. HGT-1410 will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will initially receive the same dose of HGT-1410 they received 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)

Patients assigned to Group 1 had their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

The study drug will be administered through an IDDD.

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

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

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

6.3 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT HGT-1410 dosing for safety assessments, designated Day 1, on each HGT-1410 treatment week, and if no safety concerns exist, will receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details).

6.3.1 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for clinical laboratory evaluation and potential biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling. Site personnel should refer to the operations manual for instructions on the use of topical anesthesia prior to accessing the IDDD reservoir.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the IDDD Manual and Section 6.3.2. Intrathecal Administration of HGT-1410

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive HGT-1410 via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 4 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

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

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

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.3.2). The investigation and management of a malfunctioning IDDD is detailed in the PORT-A-CATH or SOPH-A-PORT IFUs. Partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.3.2 Administration of HGT-1410 via Lumbar Puncture Guidance Concerning Performance of Lumbar Puncture for Study Drug Administration and Cerebrospinal Fluid Sample Collection

It is intended that the IDDD will be used to deliver all IT injections of study drug and to obtain CSF samples. If the IDDD appears to be nonfunctional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD manual (s), which provides details on the investigation and management of any IDDD-related issues. This may include possible partial revision or complete replacement of the IDDD as indicated. If the nonfunctional IDDD is a PORT-A-CATH device, then it will be replaced by a SOPH-A-PORT Mini S device.

If there are medical contra-indication to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are

identified by the investigator, up to 12 consecutive lumbar punctures may be performed across studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD will be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.

Continued treatment via repeat lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases of patients where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

6.4 Method of Assigning Patients to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with HGT-1410. Patients will initially receive the same dose of HGT-1410 they received in Study HGT-SAN-055. Patients assigned to Group 1 (10 mg once per month [Q4W]) had their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

6.5 Blinding

Not applicable; as this trial is not blinded.

6.6 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Dictionary (WHO-DD).

6.7 Restrictions

6.7.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.
- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device

implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than HGT-1410 or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.7.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.7.3 Patient Activity Restrictions

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

6.8 Treatment Compliance

HGT-1410 is administered under controlled conditions by the investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.9 Packaging and Labeling

6.9.1 Drug Product

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of HGT-1410. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminium seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9.2 SOPH-A-PORT Mini S Access Port

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

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

6.10 Storage and Accountability

6.10.1 Investigational Product

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

All HGT-1410 study drug delivered to an investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the sponsor or its designee or disposed of after sponsor approval per site policy after study completion.

6.10.2 Intrathecal Drug Delivery Device

6.10.2.1 PORT-A-CATH IDDD

Please refer to the operations manual for return instructions.

6.10.2.2 SOPH-A-PORT Mini S IDDD

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

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

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

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

6.11 Investigational Product Retention at Study Site

All HGT-1410 study drug delivered to an investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the sponsor or its designee or disposed of after sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory Manual.

7.2 Physical Examination

A full physical examination or a symptom-directed physical examination of each patient will be performed at time points detailed in Appendix 1 Schedule of Events.

Any changes from the screening physical examination will be captured as AEs in the eCRF. If the patient experiences an AE associated with genitourinary evaluation, the patient may have the genitourinary evaluation performed by their primary care provider and a follow-up report will be sent to the investigator. Therefore, the genitourinary evaluation may not need to be performed again if the examination occurred within the visit window for that time point.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.9). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological (symptom directed and at least every 12 months)
- Endocrine
- Genitourinary (as per referring physician)

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory Manual. The conduct of a clinical trial in an extremely rare disease such as MPS IIIA provides a unique opportunity to collect samples for potential biomarker research. In the context of this study, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of the MPS IIIA pathogenic process, or a pharmacologic response to experimental therapy with HGT-1410. In addition to exploration of potential biomarkers, as part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.7.4 Serum Anti-rhHNS Antibody and Sample Storage

Blood samples will be collected and evaluated at Shire or Shire-designated laboratories for the determination of anti-rhHNS antibodies.-Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory Manual.

7.7.5 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the investigator).

7.7.5.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.7.5.2 Urine Glycosaminoglycans

A urine sample will be collected for the determination of GAG (including heparan sulfate and heparan sulfate derivatives) and the analysis will be performed at Shire, or Shire designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.6 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.6.1, 7.7.6.2, and 7.7.6.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or ribonucleic acid (RNA) may become used as they become available in the future.

7.7.6.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.6.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire designated laboratories.

7.7.6.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of anti-rhHNS antibodies at Shire or Shire designated laboratories.

7.7.6.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of MPS exploratory biomarkers at Shire or Shire-designated laboratories.

7.7.7 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory Manual to be provided by Shire.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the investigator believes causes significant conductive hearing loss and impairment of daily living, the investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Device Data

[redacted]

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. After full approval of protocol Amendment 4, all IDDD replacements will be made with the SOPH-A-PORT IDDD. If the IDDD device is a PORT-A-CATH IDDD, it will be replaced by a SOPH-A PORT IDDD. Management details for the PORT-A- CATH IDDD or for the SOPH-A PORT IDDD are provided in the respective device's IFU. Procedures for implantation are detailed in the relevant device's Instructions for Use Manual and in the training materials provided by Shire. The patient will be under general anesthesia for this procedure. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly, and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the IDDD Manual).

A post-operative check of the IDDD and incision will be performed on Day 4 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Device Related Study Procedures

7.13.1 IDDD Implantation or Revision Procedures

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

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

Details of the implantation/revision and malfunctions/failure for the SOPH-A-PORT will be documented on the patient's eCRF.

7.13.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

A postoperative x-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, as needed, throughout the study. If the patient is to receive intrathecal HGT-1410 beyond the end of the study, an X-ray will be performed at the end of the study to verify that the IDDD is in the correct position. At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during the study, additional x-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an X-ray may be performed to assess the potential cause of malfunction. Fluoroscopy may be used during device implant or revision procedures.

7.13.3 CSF Sampling Procedure

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

7.13.4 Device Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's IFU due to a device-related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

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

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

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

If the IT space is not accessible via the IDDD, study drug may be administered by LP up to 5 times.

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

7.14 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision

or replacement is done. Following implementation of Amendment 6 the CSF opening pressure measurement will not be required with the LP.

7.15 Dispensing Study Drug

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. HGT-1410 will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, HGT-1410 may be administered via LP. See Section 6.3.2 for details.

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

7.16 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.17 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

7.18 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.19 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.20 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.20.1, 7.20.2, and 7.20.3.

7.20.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age.

7.20.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being.

7.20.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.21 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.22 Adverse Events

7.22.1 Definitions of Adverse Events and Serious Adverse Events

7.22.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

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

Throughout the study, the investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to study drug. The investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All AEs should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of HGT-1410. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to HGT-1410 caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of HGT-1410 to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal HGT-1410 therapy to date.

7.22.1.2 Potential Adverse Events: Intrathecal recombinant human heparan N-sulfatase

ADVERSE EVENTS RELATED TO THE DIRECT DELIVERY OF HGT-1410 TO THE CNS THROUGH INTRATHECAL ADMINISTRATION

Examples of AEs observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory paresthesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time

ADVERSE EVENTS DUE TO SYSTEMIC EXPOSURE TO HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

7.22.1.3 Infusion/Hypersensitivity Reactions and Management

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

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

- Treatment with medications such as antihistamines, antipyretics, and/or corticosteroids
- Stopping and resuming treatment

- Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required

7.22.1.4 IDDD-related Adverse Events

IDDD ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site, or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A malfunction of the device (defined in Section 7.22.2.2) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section 7.22.2.3), the device may need to be replaced or repaired. Hospitalization for such a procedure will be reported as a serious adverse event (SAE). Details of the cause of IDDD malfunction or failure will be recorded on the Device Malfunction/Failure CRF. A list of the more common IDDD AEs is included in Appendix 3.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS

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

IT ADMINISTRATION PROCESS ADVERSE EVENTS

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

RISKS ASSOCIATED WITH ANESTHESIA REQUIRED FOR STUDY ASSESSMENTS

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

RISKS ASSOCIATED WITH LUMBAR PUNCTURE

Risks associated with LP include pain at the injection site, infection, meningitis, encephalitis, cerebritis, failed procedure, bleeding, dural tears, spinal headache, spinal fluid leakage, nerve damage, and focal and non-focal neurological injury (including paralysis). Patients may require

anesthesia prior to an LP. Risks from anesthesia are discussed separately in this section (Section 7.22.1.4).

7.22.1.5 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization. Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s). *Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs."*

2. Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21CFR812.3[s] or other regulatory requirements, as applicable).

7.22.2 Device-Associated Definitions

7.22.2.1 Device Revision (Partial and Full)

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

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

7.22.2.2 Device Malfunction

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

7.22.2.3 Device Failure

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

7.22.2.4 Device Adjustment

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

7.22.3 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page. Adverse events are graded as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3 Adverse Event Severity

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

7.22.4 Relatedness of Adverse Events and Serious Adverse Events

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

Table 7-4 Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	Unrelated to study drug, device, device surgical procedure, or IT administration process.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of study drug, device, device surgical procedure, or IT administration process but which could also be explained by concurrent disease or other drugs or chemicals.

Table 7-4 Adverse Event Relatedness

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

7.22.5 Procedures for Recording and Reporting Adverse Events

7.22.5.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE regardless of relationship to investigational product, device, device surgical procedure, or IT administration process that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the investigator as to the relationship of the SAE to the investigational product and or device. The investigator will promptly supply all information identified and requested by the sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device, or procedure.

The investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted] United Kingdom OR
United States FAX: [redacted]
Email: [redacted]

AND

Shire HGT Medical Monitor:
FAX: [redacted] (United States)

The investigator may also call the medical monitor directly (optional):

Shire HGT Medical Monitor: [redacted], DO
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted] (24 hour access)
Email: [redacted]
AND
Clinical Project Manager CC'd: [redacted]

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

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

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

The investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the sponsor to ensure that each investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The investigator or sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the sponsor will also notify the investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication

7.22.5.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due

regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. The relationship of each AE to study medication must be recorded. In addition AEs may be considered to be related to the IDDD, the IDDD surgical procedure, or the IT administration process. Since the AE may be deemed to be related to more than one of these factors, as many of these IDDD-related options as apply should be indicated on the eCRF.

7.22.5.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. In an emergency situation, the investigator should contact the Shire Medical Monitor (see Section 7.22.5.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The investigator or other physician in attendance in such an emergency must contact the Shire Medical Monitor as soon as possible.

The investigator, along with the Shire Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.23 Abuse, Overdose and Medication Errors

Abuse, misuse, overdose or medication error must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.22.

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed **by the protocol)**
- **Overdose –** Overdosage with adverse clinical consequences is not anticipated with the use of HGT-1410. Additionally, HGT-1410 will be given in a clinical setting by a health care provider.

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

7.24 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered by the sponsor to be possibly, probably, or definitely related to study drug **or the IDDD**, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered by the sponsor to be possibly, probably, or definitely related to the study drug **or the IDDD**, then the site will be instructed to halt further HGT-1410 administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.25 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of HGT-1410 throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of HGT-1410. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a pregnancy test is positive the patient will be discontinued from the study, and the investigator must contact the Shire Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.26 Removal of Patients from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

A patient's participation in the study may be discontinued at any time at the discretion of the investigator, sponsor, or medical monitor. The following may be justifiable reasons for the investigator, sponsor, or medical monitor to remove a patient from the study:

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.
- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit.

Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient will be scheduled for the removal of the IDDD.

7.27 Other Study Procedures

This section is not applicable.

7.28 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit – Main Site

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last HGT-1410 administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of HGT-1410 in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the investigator. A decision about enrollment will be made following discussion with the medical monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal HGT-1410 dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine GAG, including heparan sulfate and heparan sulfate derivatives
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (serum and CSF)
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
- ABR
- MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments performed prior to the administration of anesthesia)
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments – Main or Local Site

Patients will receive HGT-1410 IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs (may be performed on Day 2 if feasible for the patient to arrive at the study site early in the day and if deemed clinically appropriate by the investigator)
- Hematology (after Month 54 frequency reduced to Q3 Months)
- Serum chemistry (after Month 54 frequency reduced to Q3 Months)
- Urinalysis (after Month 54 frequency reduced to Q3 Months)
- Pregnancy testing (applicable females only)
- Neurological examination (to be performed if symptom directed prior to the administration of anesthesia and the HGT-1410 IT injection and at a minimum of every 12 months)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal HGT-1410 treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, 54, 60, 72, 84, 96, AND 102

- Head circumference
- Visual and hearing assessments
- Urine GAG, including heparan sulfate and heparan sulfate derivatives (performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54)
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54)
- ABR (not performed after Month 54, ie not on Months 60, 66, 72, 84, 96, or 102)
- MRI of the head
- Full neurodevelopmental testing, including VABS-II (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QoL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of HGT-1410

Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the investigator.

- Physical examination (after Month 54 the full physical examination will be performed on an annual basis at Months 66, 78, 90, and 102. The remainder of the physical examinations will be symptom-directed.)
- ECG (performed following IT study drug injection)(after Month 54 performed Q3 months)
- Vital signs (to be performed at the discretion of the investigator)
- CSF sample collection (obtained prior to IT study drug injection)
- HGT-1410 IT injection (Day 2 ±2 days)
- Neurological examination (to be performed if symptom directed and at a minimum of every 12 months)
- Concomitant medications, therapies, and procedures
- AE assessments

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

8.3 End of Study/Early Termination Procedures: Month 103 – Main Site

Patients who complete the study or who discontinue prior to the end of the study, will have EOS assessments performed 30 (±7 days) after their last dose of HGT-1410.

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Patients will have the IDDD removed when they discontinue from the study, unless the patient is continuing to receive treatment through another mechanism (eg, expanded access, commercially available).

- Physical examination
- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Pregnancy testing (applicable females only)
- Urine GAG, including heparan sulfate and heparan sulfate derivatives
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (serum and CSF)
- MRI of the head (unless performed at Month 102)
- CSF sample collection (unless performed at Month 102)
- Neurological examination
- Full neurodevelopmental testing, including VABS-II
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- Infant toddler QoL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

All patients who discontinue the study early will have their IDDD removed.

Patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 104

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures
- AE assessments

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of HGT-1410 in patients with MPS IIIA. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables, and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

No a priori hypotheses will be tested. Exploratory hypotheses may emerge from the data analysis, in which case, appropriate testing methods will be applied and specified in the statistical analysis plan.

There are no formal hypotheses associated with the evaluation of the safety and performance of the IDDD device (SOPH-A-PORT Mini S). All analyses of device safety and performance will be descriptive and no statistical testing will be performed. Device related analyses will be based on patients for whom the device implant procedure was performed and are described in the sections below.

10.2 Determination of Sample Size

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

10.3 Analysis Populations

The primary analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. This population will be used to perform both safety and efficacy analyses. The collection of detailed data pertaining to the SOPH-A-PORT mini S will permit device-related analyses to be conducted in the subset of patients in the primary analysis population who had the SOPH-A-PORT Mini S implant procedure performed**.**

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of AEs, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients who had an IDDD surgical procedure and/or received administration of HGT-1410 will be included in the safety analysis.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each dose group, the number and percentage of patients having any AE, having an AE in system organ class, and having each individual AE. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events , defined as all AEs from the time of the surgery for IDDD implantation to the last follow up contact, ie, 30 days after the last HGT-1410 administration, (new or worsened from baseline) will be summarized by system organ class, severity, type of adverse event and relationship to trial medication/procedure.

Treatment-emergent AEs deemed related to HGT-1410 administration will be summarized separately.

IDDD and procedure-related AEs will be summarized within system organ class by preferred term. IDDD and procedure-related AEs will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure (including post-implant infections) and IT administration process. These summaries will be presented by device and overall, as appropriate.

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis and CSF) results will be presented in summary tables by evaluation visit. Changes from baseline will be summarized for each post-baseline visit. Each laboratory result will be categorized as a patient having had (1) an Abnormal and Clinically Significant (CS) value at any time, (2) no CS values at any time but had at least one Abnormal and not CS (NCS) value, and (3) no CS or NCS values at any time; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any time 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.

The observed values and changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

The observed values and changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by number and percentage of positive and negative specimens by evaluation visit, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.2 Other Observations Related to Safety

10.6.2.1 IDDD Performance

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

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

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

10.6.3 Secondary Analysis

10.6.3.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of HGT-1410 administration on QoL measures will be examined by presenting mean change from baseline by dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.3.2 Pharmacodynamic Analyses

To determine the effects of HGT-1410 administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparan sulfate reduction (in CSF) will be examined using mean change and the corresponding 95% confidence interval. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

10.6.4 Interim Analysis

No formal analysis or interim statistical testing for early stopping of the trial is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting, publication, or general planning purposes.

The planned final analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

The study will be monitored by the sponsor or its designee. On site monitoring will be performed by a representative of the sponsor (clinical study monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted

according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

Before Shire initiates the trial (ie, obtains informed consent [assent if applicable] from the first patient), it is the responsibility of the investigator to ensure that the following documents are available to Shire or their designee:

- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of investigator and sub-investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire. All trial documents will be available in a Trial Master File (TMF) at the investigator/trial site and at Shire.

11.8 Device Failure Review Process

The final cause for device failures will be reviewed by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

11.9 Protocol Violations/Deviations

The investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the sponsor or an investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire and the investigators. In addition, a decision on the part of Shire to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the investigator to enter patients at an acceptable rate.
- Insufficient adherence by the investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.7.7).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study in a timely manner.

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

Shire may perform analyses of interim and/or final locked study data for the purpose of publication.

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08 February 2016

Appendix 1 Schedule of Events

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)						
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	
Informed Consent/Enrollment		●						
Physical Examination	●	●[p]	●[p]	●[p]				
Symptom-Directed Physical Examination		●[p]	●[p]				●	
Neurological Examination[h]	●	●[s]	●[s]				●	
Height and Weight	●	●					●	
Head Circumference	●			●			●	
Visual and Hearing Assessment				●			●	
ECG	●		●[b]				●	
Vital Signs	●	●[s]	●[s]				●	
Hematology	●	●					●	
Serum Chemistry	●	●					●	
anti-rhHNS antibody testing (serum)[k]	●			●[t]	●[t]		●	
Plasma storage for biomarkers	●	●		●			●	
Pregnancy Testing[l]	●	●					●	
Urinalysis	●	●					●	

08 February 2016

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)						
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	
Urine GAGs	●			●[t]	●[t]		●	
Leukocyte pellet preparation[m]	●							
CSF chemistry and cell counts[c]	●	●					●	
CSF sample storage[c,o]	●	●					●	
CSF Heparan Sulfate and Heparan Sulfate Derivatives[c]	●			●[t]	●[t]	●		
Anti-rhHNS antibody testing (CSF)[c]	●			●[t]	●[t]		●	
Auditory Brainstem Response (ABR)[q]	●			●				
MRI of the Head	●			●			●[n]	
HGT-1410 dosing: every 28 (±7) days[d,g]			●					
Full Neurodevelopmental Testing[i]	●			●			●	
Children's Sleep Habits Rating Scale	●			●			●	
Child Health Questionnaire-50	●			●			●	
Child Health Questionnaire-87	●			●			●	
Infant Toddler QOL Questionnaire	●			●			●	
Concomitant Medications, Therapies, and Procedures	●	●	●				●	●

08 February 2016

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)					
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	
Adverse Event Monitoring	●	●	●				●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; EOS = end of study ; ECG = electrocardiogram; IT = intrathecal; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as presented here at Month 102, corresponds to Month 102 in HGT-SAN-067, but represents a total of 102 months of study treatment (102 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug, after Month 54 it is to be performed every 3 months.

[c] CSF samples will be obtained according to the process within the study laboratory manual. An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of HGT-1410 and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or an LP may be performed.

[d] Patients may be discharged as early as 4 hours post HGT-1410 infusion (ie, on Day 2) when deemed clinically stable by the investigator.

[e] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[f] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] The neurological exam should not occur sooner than 4 hours after administration of study drug or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

[i] Full neurodevelopmental testing includes an assessment with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II).

[j] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled HGT-1410 IT dose.

[k] Blood sample drawn before IT injection of HGT-1410.

08 February 2016

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)					
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	

[l] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[m] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

[n] These assessments are not to be performed at an EOS visit conducted at Month 103 if they were performed at the Month 102 visit.

[o] CSF samples will be tested for MPS exploratory biomarkers, and possibly extractables and leachables.

[p] After Month 54 the Symptom-Directed PE is to be done monthly. Full PE is done monthly to Month 54 and then at least yearly (ie, Months 66, 78, 90, and 102), or more frequently at the investigator's discretion. Genitourinary AEs may be evaluated by the patient's primary care physician and a follow-up report will be sent to the study site.

[q] ABR will not be performed after Month 54.

[r] Informed consent will be obtained at Screening and Month 54.

[s] These Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

[t] Urine GAG, including heparan sulfate and heparan sulfate derivatives, and anti-rhHNS antibody testing will be performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54); these assessments must be performed at the main site.

Appendix 2 Neurodevelopmental and Behavioural Assessments

Tables A2-1 and A2-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table A2-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table A2-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child’s abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III)[23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]

Purpose:

The KABC-II measures a child’s cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery’s results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Expected Adverse Device Effects

Procedure-Related Complications

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

Intrathecal Access Complications

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

System-Related Complications

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

Appendix 4 Protocol Amendment 7 Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol HGT-SAN-067 has been amended to extend the study and provide treatment with HGT-1410 for an additional 24 months (to Month 103 from start of study HGT-SAN-055), and to include the addition of local (satellite) sites to reduce the burden imposed by monthly travel. [redacted] replaced [redacted] in the role of Medical Monitor. Language regarding infusion related reactions and risk language for anesthesia and lumbar puncture was added. Other clarifications related to the IDDD use were added, including the allowance of device explanation at local sites. Language clarifying some of the assessment language, including neurocognitive and vital sign assessment performance on the same day as drug administration, and genitourinary assessment may be performed by primary care provider (with follow-up report to investigator) if an AE associated with genitourinary evaluation occurs. Language was also added to allow for interim and final locked study data publications.

Previous Amendment: Amendment 6; 10 July 2014

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: Replacement of [redacted] by [redacted] as Medical Monitor
Section impacted by this change: Title page
Other sections impacted by this change: Section 7.22.5.1, Appendix 5 Signature Page

Change: Removal of informed consent at Month 54
Section impacted by this change: Synopsis
Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures ~~and again at Month 54~~.
Other sections impacted by this change: None

Change: Addition of language to allow for local (satellite) sites
Section impacted by this change: Section 4.1
Primarily main sites will be utilized; however, the sponsor and investigator will consider the feasibility of transitioning the patient's IT dosing to local sites to reduce the burden imposed by travel. At Month 18 (12 months after study start), patients that already received IT dosing at the main site may be eligible to transfer to a local site if in the opinion of the investigator there are no safety or medical concerns precluding this transition. Subsequent IT injections of HGT-4110 may be performed

at either the main site or the local site. The local sites will be selected and approved by the sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: the main site may serve as a local site as needed; and in this case, the main site will follow the assessments scheduled for a local site). The qualification requirements for physicians at local sites will be identical to those for the main sites. Local sites will be trained if inexperienced with IT administration via an IDDD. Patients will be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the investigator. Dosing by IT injection may take place at the main site, rather than local site, if scheduled study assessments include MRI and cognitive assessments. Patients must review and agree to written informed consent/assent from the local site to participate in study procedures to be conducted at the local site prior to the conduct of these procedures.
Other sections impacted by this change: Section 6.2, Section 8.1, Section 8.2, Appendix 1 Table A1-1 Schedule of Events

Change: Last planned administration of HGT-1410 designated as Month 102, EOS study procedures designated as Month 103, Safety Follow-up designated as Month 104
Section impacted by this change: Section 4.1
All patients will have an EOS visit 30 (±7) days following their last administration of HGT-1410 (ie, Month ~~78~~**102**). All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit (ie, Month ~~79~~**103**) to collect updated information on AEs and concomitant medications, therapies, and procedures.
Other sections impacted by this change: Synopsis; Section 8.2, Section 8.3, Section 8.4, Appendix 1 Table A1-1 Schedule of Events

Change: Study duration changed from 6 years to 8 years
Section impacted by this change: Section 4.3
The study duration ~~will be 6~~ **allows patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in Study HGT-SAN-067 to receive treatment with HGT-1410 up to 8** years.
Other sections impacted by this change: Synopsis; Appendix 1 Table A1-1 Schedule of Events

Change: Allowance of genitourinary evaluation by primary care physician if AE associated with genitourinary evaluation
Section impacted by this change: Section 7.2
Any changes from the screening physical examination will be captured as AEs in the eCRF. **If the patient experiences an AE associated with genitourinary evaluation, the patient may have the genitourinary evaluation performed by their primary care provider and a follow-up report will be sent to the investigator. Therefore, the genitourinary evaluation may not need to be performed again if the examination occurred within the visit window for that time point.**
Other sections impacted by this change: Appendix 1 Table A1-1 Schedule of Events

Change: Additional of language to allow device explanation to be performed at local sites
Section impacted by this change: Section 7.13.1
The IDDD will be surgically implanted or revised at the clinical site. Procedures for implantation and revision are detailed in the device's IFU. Standard hospital procedures for surgery will be followed; the patient will be under general anesthesia for this procedure. **It is planned that device explantation will occur at the main site unless urgent device removal is medically indicated requiring the procedure to be performed locally or patient travel to the main site is medically inadvisable.**
Other sections impacted by this change: Section 4.2

Change: Addition of language regarding infusion/hypersensitivity reactions and management
Section impacted by this change: Section 7.22.1.3
7.22.1.3 Infusion/Hypersensitivity Reactions and Management **Infusions of proteins can be associated with reactions to the infusion that may or may not be immune-mediated (hypersensitivity reactions). Thus, potential reactions to the infusion of investigational drug are unpredictable. It is often difficult to clinically distinguish infusion reactions from hypersensitivity reactions. Symptoms may include headache, fever, sensory paresthesias (including feeling of warmth, tingling, or pain), rash, pruritus, or autonomic symptoms, such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection over time.**

The management of infusion reactions and hypersensitivity reactions is similar. The following steps may be taken, at the discretion of the investigator, in the event of a suspected infusion related/hypersensitivity reaction and the management of such reactions should be based on the severity of the reaction: • **Treatment with medications such as antihistamines, antipyretics, and/or corticosteroids** • **Stopping and resuming treatment** • **Pretreatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required**
Other sections impacted by this change: None

Change: Addition of risk language for anesthesia and lumbar puncture
Section impacted by this change: Section 7.22.1.4
RISKS ASSOCIATED WITH ANESTHESIA REQUIRED FOR STUDY ASSESSMENTS **The use of an IDDD has been chosen to minimize the risks inherent in utilizing novel delivery systems and to alleviate the need for multiple administrations of anesthesia required for drug injection via repeated LP. The risks from anesthesia include respiratory depression, aspiration, cardiac events, hypoxia, hypotension and hypertension, difficult intubations and extubations, stroke, rapid changes in body temperature, laryngospasm or laryngeal edema, allergic reaction, and death. Patients will be closely monitored for changes in vital signs and related events.** **RISKS ASSOCIATED WITH LUMBAR PUNCTURE** **Risks associated with LP include pain at the injection site, infection, meningitis, encephalitis, cerebritis, failed procedure, bleeding, dural tears, spinal headache, spinal fluid leakage, nerve damage, and focal and non-focal neurological injury (including paralysis). Patients may require anesthesia prior to an LP. Risks from anesthesia are discussed separately in this section (Section 7.22.1.4).**
Other sections impacted by this change: None

Change: Addition of definition for device adjustment
Section impacted by this change: Section 7.22.2.4
7.22.2.4 Device Adjustment **Surgery of the device which does not result in partial or complete device revision or removal (eg, surgical exploration only or placement of additional sutures, tissue glue, and/or fascial repair).**
Other sections impacted by this change: None

Change: Clarification regarding study assessments, including vital signs, neurological examination, MRI of the head, and physical examination; and a change in timing to the ECG (to Q12)
Section impacted by this change: Section 8.2.1
8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose • Physical examination • Height and weight • Vital signs **(may be performed on Day 2 if feasible for the patient to arrive at the study site early in the day and if deemed clinically appropriate by the investigator)** • Hematology (after Month 54 frequency reduced to Q3 Months) • Serum chemistry (after Month 54 frequency reduced to Q3 Months) • Urinalysis (after Month 54 frequency reduced to Q3 Months) • Pregnancy testing (applicable females only) • Neurological examination (**to be** performed **if symptom directed** prior to the administration of anesthesia and the HGT-1410 IT injection **and at a minimum of every 12 months**) … **DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, 54, ~~6~~6, 60, 72, 84, 96, AND ~~7~~8102** • Head circumference • Visual and hearing assessments • Urine GAG, including heparan sulfate and heparan sulfate derivatives (~~also~~performed at Month**s 60, 66** ~~and ,Month~~ 72**, 78, 84, 90,** ~~Month~~ **and 96**, ie, Q6 Months following Month 54) • Plasma collection for biomarkers • Anti-rhHNS antibody testing (~~also~~performed at Month**s 60, 66,**~~78 and Month~~ **72, 78, 84, 90, and 96,** ie, Q6 Months following Month 54) • ABR (not performed after Month 54, ie not on Month**s 60,** 66**, 72, 84, 96,** or ~~7~~8**102**) • MRI of the head

…

8.2.1.2 Day 2 (±2 days) Assessments and Administration of HGT-1410

Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the investigator.

- Physical examination (after Month 54 the full physical examination will be performed **on an annual basis** at Months ~~54,~~ 66, ~~and~~ 78**, 90, and 102**. The remainder of the physical examinations will be symptom-directed.)
- ECG (performed following IT study drug injection)(after Month 54 performed Q3 months)
- Vital signs **(to be performed at the discretion of the investigator)**
- CSF sample collection (obtained prior to IT study drug injection)
- HGT-1410 IT injection (Day 2 ±2 days)
- Neurological examination **(to be performed if symptom directed and at a minimum of every 12 months)**

…

Other sections impacted by this change: Synopsis; Section 4.1; Appendix 1 Table A1-1 Schedule of Events

Change: Clarification regarding the inclusion of ECG, plasma storage for biomarkers, and pregnancy testing as EOS assessments

Section impacted by this change: Section 8.3

Other sections impacted by this change: Appendix 1 Table A1-1 Schedule of Events

Change: Addition of language to allow for analyses of interim/final data for purpose of publication

Section impacted by this change: Section 11.15

Shire may perform analyses of interim and/or final locked study data for the purpose of publication.

Other sections impacted by this change: Section 10.6.4

Change: Clarification in schedule regarding Day 1/Day 2 neurocognitive and vital sign assessments, and additional assessments at Months 66, 78, and 90 for urine GAG, including heparin sulfate and heparin sulfate derivatives, and anti-rhHNS antibody testing
Section impacted by this change: Appendix 1 Table A1-1 Schedule of Events
Addition of footnotes: **s These Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.** **t Urine GAG, including heparan sulfate and heparan sulfate derivatives, and anti-rhHNS antibody testing will be performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54); these assessments must be performed at the main site.**
Other sections impacted by this change: None

Appendix 5 Protocol Signature Page

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 Amendment 7
Final Date:	21 June 2010
Amendment 1 Date:	22 January 2011
Amendment 2 Date:	13 January 2012
Amendment 3 Date:	28 August 2012
Amendment 4 Date:	3 May 2013
Amendment 5 Date:	17 January 2014
Amendment 6 Date:	10 July 2014
Amendment 7 Date:	08 February 2016

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

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

[redacted] DO
Printed Name

Appendix 6 The National Cancer Institute Common Terminology Criteria version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

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Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may ***not*** be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY						Page 1 of 1
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW						Page 1 of 1
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*:	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome						
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*:	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia						
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic.						
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL						Page 1 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL						Page 2 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL						Page 3 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						Page 4 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL						Page 5 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL						Page 6 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL						Page 7 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						Page 8 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						Page 9 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT						Page 1 of 1
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING						Page 1 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 2 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

Page 3 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS						Page 1 of 1
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.						
ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

Page 3 of 3

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 1 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						Page 2 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE						Page 3 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY						Page 1 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY						Page 2 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						Page 3 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY						Page 4 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death

NEUROLOGY						Page 5 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY						Page 1 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY						Page 2 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						Page 3 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a “late effect” seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select.*						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

Page 2 of 2

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES							Page 1 of 2
		Grade					
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**	
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.							
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.							
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.							
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death	
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.							
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.							
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death	
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.							
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.							
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.							
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death	
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.							
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.							

SYNDROMES						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

Clinical Trial Protocol: HGT-SAN-067

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
Study Phase:	I/II
Product Name:	Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)
Device Names:	SOPH-A-PORT® Mini S, Implantable Access Port, Spinal, Mini Unattached, with Guidewire and PORT-A-CATH® II Low Profile™ *Intrathecal Implantable Access System* (Smiths device)
EudraCT Number:	2010-021348-16
Indication:	Sanfilippo Syndrome A
Investigators:	Multicenter
Sponsor:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421, United States
Medical Monitor:	[redacted], DO, [redacted]

	Date
Original Protocol:	21 June 2010
Amendment 1:	27 January 2011
Amendment 2:	13 January 2012
Amendment 3:	28 August 2012
Amendment 4:	3 May 2013
Amendment 5:	17 January 2014
Amendment 6:	10 July 2014
Amendment 7:	08 February 2016
Amendment 8:	01 February 2017

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Sponsor:

Shire Human Genetic Therapies, Inc.

300 Shire Way

Lexington, MA 02421, United States

[redacted]

Name of Finished Product:

Recombinant human heparan N-sulfatase (rhHNS, HGT-1410)

Name of Active Ingredient:

rhHNS, HGT-1410

Name of Inactive Ingredient:

N/A

Names of Devices:

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

and

PORT-A-CATH® II Low Profile™ Intrathecal Implantable Access System (PORT-A-CATH)

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

Study Phase: I/II

Device, Intended Use

The SOPH-A-PORT Mini S is a system intended for implantation by physicians. The SOPH-A-PORT Mini S, once implanted, allows healthcare personnel to administer HGT-1410 indicated for intrathecal delivery intermittently over a long period of time.

Prior to approval of Amendment 4, patients were implanted with a PORT-A-CATH (Smith's device). After approval of Amendment 4 all PORT-A-CATH IDDDs requiring revision or replacement will be replaced with a SOPH-A-PORT at a time judged appropriate by the investigator.

Study Objectives:

Primary Objective:

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients with Sanfilippo Syndrome Type A (MPS IIIA) who received HGT-1410 via a surgically implanted intrathecal drug delivery device (IDDD) in study HGT-SAN-055 and elected to continue therapy

in study HGT-SAN-067.

Secondary Objectives:

The secondary objectives of this study are:

- 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.

Study Endpoints:

Primary Endpoints:

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

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

Secondary Endpoints:

The secondary endpoints of this study are to collect over an extended treatment period (as change from baseline) clinical and potential surrogate biomarker efficacy data:

- Standardized neurocognitive and behavioral assessments, Sanfilippo-specific behavioral rating scales, gross and fine motor assessments, functional adaptive rating scales, quality of life 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 and heparan sulfate derivatives in CSF and glycosaminoglycans (GAG), including heparan sulfate and heparan sulfate derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), Brainstem Auditory Evoked Potentials).

Study Design:

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 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with 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. Initially, patients will continue in the same treatment group they were assigned to in the HGT-SAN-055 study. Following approval of Protocol Amendment 4, patients in the 10 mg group had their dose increased to 45 mg per month.

For nomenclature of chronology purposes, the Baseline Visit for this extension study will be considered to be the first day the patient received his/her IT dose of HGT-1410 in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent must be obtained prior to performing any study-related procedures that are specific to HGT-SAN-067.

Informed consent will be provided by the patient's parent(s)/legally authorized representative(s) prior to the start of the extension study procedures. Informed consent may be obtained anytime from week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the investigator.

All patients will have received a series of standardized neurodevelopment assessments in the HGT-SAN-055 study. These assessments will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067, during the treatment period, with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments would be performed after the original assessments (those previously used in study HGT-SAN-055) have been carried out, during the treatment period of the study. An MRI of the head will be performed at Months 12, 24, 36, 54, 60, 72, 84, 96, and 102 and ABR testing will be performed at Months 12, 24, and 36 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study), during the treatment period. Note: X-rays may be performed to investigate device malfunction, migration, and to verify correct catheter and port placement following surgical implantation or revision. In addition, fluoroscopy should be employed intraoperatively to guide catheter placement. Thus, patients may undergo 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 is 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 is limited to 6 exposures in any 6-month period (including time in the HGT-SAN-055).

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and that are ongoing at enrollment in HGT-SAN-067 will be captured in

the case report forms (CRFs) for study HGT-SAN-067. Specific safety stopping criteria will be applied and will be based on the types and severity of adverse events (AEs) reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit, during the treatment period, 30 (±7) days following their last administration of HGT-1410 (ie, Month 102). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child health questionnaires, and MRI.

Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, to be conducted at 30 (±7) days after the EOS visit of the treatment period (ie, Month 103) to collect updated information on AEs and concomitant medications, therapies, and procedures.

If the patient is discontinued from the study, the IDDD should be removed and a modified end of study visit should be completed within 30 days after withdrawal. These visits may be combined into one visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. If the investigator determines that the IDDD should not be removed from the patient based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit.

It is anticipated that the IDDD will be used to obtain CSF samples and to deliver administrations of HGT-1410. However, if a patient's IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the operations manual (for PORT-A-CATH) or the IDDD Manual (for SOPH-A-PORT), which describes the investigation and management of IDDD-related issues. This will include possible partial revision or complete replacement of the IDDD. As noted above, a maximum of 2 partial revisions and/or complete replacements can occur in any 6 month period. If revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period (including participation in study HGT-SAN-055), HGT-1410 will be administered via lumbar puncture (LP).

If there are medical contra-indications to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive lumbar punctures may be performed across the studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD may be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical

monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.

Continued treatment via lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

During the treatment period, 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 will be introduced for those patients requiring replacement or revision. This new device has design features anticipated to reduce complications encountered with the PORT-A-CATH IDDD device. Specific device assessments are included in the protocol to collect information with respect to information specific to SOPH-A-PORT Mini S device safety and function.

During the treatment period, patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

Patients should have the IDDD removed when they discontinue from or complete the treatment period of the study, unless the Investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

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.

An overview of the study appears in the Schedule of Events.

Study Population:

A maximum of 12 patients are planned for this study. To be eligible for participation patients will have completed all study requirements in Study HGT-SAN-055, including the EOS visit, and will have elected to continue treatment with HGT-1410.

Test Product; Dose; and Mode of Administration: Recombinant human heparan N-sulfatase (rhHNS, HGT-1410) will be administered via an IDDD according to the same dose to which the patient was assigned in HGT-SAN-055 (ie, 10 mg, 45 mg, or 90 mg monthly). Patients assigned to the 10 mg monthly dose had their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410.

Reference Therapy; Dose; and Mode of Administration:

N/A

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

Exclusion Criteria:

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has non-MPS IIIA related central nervous system (CNS) impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is a patient of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.
8. The patient is currently receiving psychotropic or other medications, which in the investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would

be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device.
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the investigator.
3. The patient has a known or suspected local or general infection.
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation.
6. The patient has a functioning CSF shunt device.
7. The patient has shown an intolerance to an implanted device.

Duration of Treatment:

The study duration allows patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in Study HGT-SAN-067 to receive treatment with HGT-1410 up to 8 years.

For those patients with a partial or full device still in place after completion of the treatment period, patients may be followed for safety up to an additional 3 years or until the device is removed in the last patient.

The LPLV will be the safety follow-up visit after the final device (partial and/or full) is removed from the last patient during the safety follow-up period.

Pharmacokinetic Variables:

N/A.

Safety Assessments:

Safety evaluations will include vital signs, physical examinations, AE assessments, electrocardiograms (ECG); serum chemistry, hematology, urine laboratory tests, and screening for antibodies to rhHNS (in CSF and serum).

Statistical Methods: The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of the trial. Data will be plotted and the mean, standard deviation, median, minimum, and maximum for each variable will be tabulated by dose group to look for gross trends over time, which may be attributed to treatment. For continuous data, 95% confidence interval (CI) around the mean will also be estimated and presented.

The analysis population consists of all eligible patients from HGT-SAN-055 who have completed Study HGT-SAN-055 and agreed to participate in this extension study. Safety analyses will be performed using the above mentioned population. The data will be presented by dose group.

Date of Original Protocol: 21 June 2010

Date of Amendment 8: 01 February 2017

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABR	auditory brainstem response
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
βhCG	human chorionic gonadotropin
BSID-III	Bayley Scales of Infant Development, Third Edition
BBB	blood brain barrier
BUN	blood urea nitrogen
Ca	calcium
CE	Conformité Européenne
CFR	Code of Federal Regulations
CHQ-50	Child Health Questionnaire™ Parent Form 50
CHQ-87	Child Health Questionnaire™ Child Form 87
CK	creatine kinase
Cl	chloride
CNS	central nervous system
CO_2	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CRO	contract research organization
CRIM	cross-reacting immunologic material
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture

Abbreviation	Definition
ERT	enzyme replacement therapy
EOS	end of study
EOW	every other week
EU	European Union
FDA	Food and Drug Administration
FPSS/TDS	Four-Point Scoring System/Total Disability Score
GAG	glycosaminoglycan
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
Hct	hematocrit
Hgb	hemoglobin
HS	heparan sulfate
ICH	International Conference on Harmonization
IDDD	intrathecal drug delivery device
IEC	Independent Ethics Committee
IFU	instructions for use
IND	Investigational New Drug
IRB	Institutional Review Board
IT	intrathecal
ITQOL	Infant Toddler Quality of Life Questionnaire™
IV	intravenous
K	potassium
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LDH	lactic dehydrogenase
LP	lumbar puncture
LSD	lysosomal storage disease
M6P	mannose-6-phosphate
MABC-2	Movement Assessment Battery for Children, Second Edition

Abbreviation	Definition
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPS	Mucopolysaccharidosis
MPS IIIA	Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A
MRI	magnetic resonance imaging
Na	sodium
NCI	National Cancer Institute
NCS	not clinically significant
PE	pressure-equalization
QoL	quality of life
Q4W	once per month
RBC	red blood cell (count)
rhHNS	recombinant human heparan N-sulfatase
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRS	The Sanfilippo Behavior Rating Scale
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
Shire HGT	Shire Human Genetic Therapies, Inc.
TMF	Trial Master File
TX	treatment
UADE	unanticipated adverse device effect
US	United States
VABS-II	Vineland Adaptive Behavior Scales
WBC	white blood cell (count)
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

The progressive and irreversible nature of lysosomal storage diseases (LSDs) present a challenge in the interpretation of clinical benefit derived from treatment in studies using enzyme replacement therapy (ERT). Any short-term improvement and/or stabilization of clinically important manifestations of the disease may be viewed as clinically meaningful. However, the demonstration of the different aspects of a long-term, clinically-meaningful improvement may be limited by the short duration of treatment in clinical studies. Extended access to treatment through extension studies provides an opportunity for further evaluation of long-term safety and clinical outcomes for treated patients. In this extension study, patients who completed study HGT-SAN-055, a phase I/II safety and dose-escalation trial, and elected to continue to receive recombinant human heparan N-sulfatase (rhHNS), will receive treatment through this extension protocol. Initially, the patient's treatment group and dosing regimen will be the same as that employed in study HGT-SAN-055. Following the analysis of data from HGT-SAN-055, patients in the lowest dose group had their dose increased to 45 mg, as outlined in Section 1.3, below.

1.1 Disease Background

Sanfilippo syndrome, or Mucopolysaccharidosis (MPS) III, is LSD caused by loss in activity of 1 of 4 enzymes necessary for degradation of the glycosaminoglycan (GAG) heparan sulfate (HS) in lysosomes. Four different subtypes (A, B, C, and D) have been identified and are each due to a specific enzyme deficiency involved in the lysosomal catabolism of HS. Mucopolysaccharidosis IIIA or Sanfilippo syndrome Type A (MPS IIIA) results from deficiency of the enzyme heparan N-sulfatase (sulfamidase). In the absence of this enzyme, intermediates of the HS degradation process accumulate in the lysosomes of neurons and glial cells, with lesser accumulation outside the brain.

MPS III is the most prevalent of all mucopolysaccharidoses, with subtype A the most common of these.[1] The birth prevalence of MPS IIIA has been estimated as 1.28 in 100,000 in Australia, 1.16 in 100,000 in the Netherlands, and 0.88 in 100,000 in Germany.[1-3] In summary, MPS IIIA is a rare genetic disorder with apparently widespread geographic distribution and an average global birth incidence of approximately 1 in 100,000.

In a recent detailed review of all MPS IIIA patients diagnosed in the Netherlands, it was reported that among 81 patients in whom information was available, first symptoms arose at a median of 2.5 years (range 0.5 to 7 years).[4] Owing to the rarity of the disease and the non-specific and often subtle nature of its initial manifestations, diagnosis is usually delayed until an average age of 4 to 4.5 years.[4, 5] Patients present a wide spectrum and severity of clinical symptoms. The central nervous system (CNS) is the most severely affected organ system in patients with MPS IIIA, evidenced by deficits in language development, motor skills, and intellectual development.[5] In addition, there are abnormal behaviors including, but not limited to, aggression and excess motor activity/hyperactivity that contribute to disturbances in sleep.[5-7] In contrast with other MPS types, the viscera are mildly affected, with transient enlargement of liver and spleen during childhood with no evidence of dysfunction. There are also reports of unexplained, recurrent and severe diarrhea.[8] Overall, individuals with MPS IIIA have a marked developmental delay and significantly reduced lifespan of 15 years of age on average.[8]

A milder variant has recently been identified with slower progression and survival to later age in approximately 10% of German patients with MPS IIIA.[9]

No effective, disease-modifying therapies are currently approved as treatments for this rare, devastating and disabling disease.

A long-range goal of Shire Human Genetic Therapies, Inc. (Shire HGT) is to develop a recombinant human sulfamidase ERT for patients with MPS IIIA. A particular problem for LSDs that damage the brain such as MPS III is how to target ERT to the brain.[10] In animal studies, ERT was administered into the cerebrospinal fluid (CSF) via an intrathecal (IT) route, because when administered intravenously (IV), it was shown to not cross the blood brain barrier (BBB) after the immediate postnatal period of life.[11, 12]

As the CNS in patients with MPS IIIA is the most severely affected body system, the main focus of the HGT-1410 clinical development program has been the development of ERT specifically for delivery directly to the CNS. Recombinant human heparan N-sulfatase has been developed specifically for delivery into the CSF via an intrathecal drug delivery device (IDDD) due to the acknowledged impermeability of the BBB to macromolecules.

Heparan N-sulfatase is a highly purified recombinant form of the naturally occurring human lysosomal enzyme sulfamidase. It is expressed from the well characterized continuous human HT-1080 cell line as a 482 amino acid peptide, following cleavage of the 20 amino acid N-terminal signal peptide. The mature protein in solution is a homodimeric glycoprotein of approximately 122 kDa, which undergoes post-translational modifications by conversion of Cys50 to formylglycine, required for enzyme activity, and glycosylation at 4 of the 5 potential N-linked glycosylation sites. The rhHNS glycans contain mannose-6-phosphate (M6P) residues which target the protein for cellular uptake and internalization in its lysosomal site of action via the membrane-bound M6P receptors.[13, 14-16]

The first precedent for intraspinal ERT was recently published and has been shown to be both safe and effective for spinal cord compression in MPS I.[17] In this study, a patient with MPS I received 4 IT doses of enzyme (Laronidase [recombinant α-L- Iduronidase]) at 1-month intervals. Safety evaluations included CSF opening pressure, serum chemistry and CSF protein, glucose and cell count, in addition to clinical efficacy studies. No changes in safety evaluations were observed.

In another recent study, a patient with MPS VI and spinal cord compression received IT injections of enzyme (Galsulfase) monthly, for 4 months. CSF analysis revealed no inflammatory reaction; no other side effects were noted.[18]

Several MPS I patients have been treated since 2005 with IT Laronidase in 2 ongoing clinical trials (clinicaltrials.gov identifiers NCT00215527 and NCT00786968) studying efficacy on spinal cord compression. No results of these trials have yet been published. However, in June 2009 a study further investigating the effectiveness of IT ERT as a treatment for another neurological symptom in MPS I, cognitive decline, was initiated (clinicaltrials.gov identifier NCT00852358).

This study is a 24-month, open label, prospective, randomized trial in 16 patients with MPS I, 6 years of age or older, who have documented evidence of cognitive decline. In this study, the clinical safety of the regimen will be assessed by adverse event (AE) monitoring, CSF laboratory assessments, and clinical evaluations. This study is ongoing; no efficacy or safety data have yet been published as of October 2011.[19]

In addition, there are 4 ongoing Shire-sponsored studies that are evaluating IT administration of ERT: A Phase I/II safety and dose escalation study of monthly idursulfase-IT injection for cognitively impaired patients with Hunter syndrome (Study HGT-HIT-045; NCT00920647), the open-label extension to this study (HGT-HIT-046); a Phase I/II ascending dose and dose frequency study of monthly IT injection of HGT-1410 in patients with Sanfilippo Syndrome Type A (Study HGT-SAN-055; NCT01155778), and the open-label extension to this study (HGT-SAN-067; NCT 01299727).

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

1.2 Nonclinical Overview

To circumvent the restriction of the BBB, HGT-1410 was administered into the CSF of rats and monkeys via an IT route. The non-clinical data demonstrate that IT administration of HGT-1410 leads to uptake by target CNS tissues with appropriate efficacy and distribution. In addition, there were no findings noted in the toxicity studies, allowing for a 6.2-fold safety margin from the results in the juvenile cynomolgus monkey. Intermittent bolus injection of HGT-1410 to the brain via the IT route of administration is hypothesized to be of benefit in stabilizing, improving, or preventing the CNS manifestations of disease.

The doses tested in the non-clinical studies adequately support the efficacy of the planned doses (10, 45 or 90 mg/month, normalized to the brain weight of the human) in the ongoing Phase I/II study, HGT-SAN-055. Specifically, in the San A mouse, the 100 μg dose corresponds to a 2.2-fold increase (per kg brain weight) from the highest anticipated human dose (90 mg) (human brain = 1 kg). The 20 μg dose given IT every other week (EOW) or monthly, for which efficacy was also observed, corresponds to a 40 mg (per kg brain weight) human dose. In the Huntaway (Sanfilippo A) dogs, the 3 mgHGT-1410 given IT weekly (corresponding to a 33 mg/kg of brain weight in man), was not only well tolerated but resulted in significant effects on biomarkers of disease activity and improved histopathology.

1.2.1 Toxicology in Monkeys

In the pivotal, 6-month IT toxicity study in juvenile cynomolgus monkeys, and the highest dose of HGT-1410 was 8.3 mg given EOW. This translates into a 138 mg/kg brain-weight dose (ie, based on a 60 g juvenile monkey brain). Since no HGT-1410-related adverse effects were noted, the nonclinical study provides for the proposed Phase I/II clinical trial a ~13.8 × safety margin

relative to the starting clinical dose (10 mg), and a 1.5× safety margin relative to the highest clinical dose (90 mg).

1.2.2 Efficacy in Murine and Canine Models of MPS IIIA

Non-clinical proof of concept efficacy studies were conducted using mouse and dog models of MPS IIIA, both of which contain naturally-occurring mutations in the HNS gene.

In the MPS IIIA mouse, direct injection into the CNS had a beneficial effect on clinical signs, impaired neurobehavioral, and the biochemical and histopathologic markers of disease activity. In Huntaway (Sanfilippo A) dogs, HGT-1410 (3 mg) given IT weekly had a significant effect on biomarkers of disease activity and improved histopathology.

Efficacy has been demonstrated at a range of doses in nonclinical mouse and canine models. In MPS IIIA mice, a dose-dependent reduction in the level of a heparan sulfate-derived monosulfate disaccharide was observed within the brain (up to 62% reduction compared with vehicle-treated mice) and spinal cord (up to 71% reduction). An ultrastructural examination revealed a reduction in lysosomal vesicle formation in various cell types and fewer (ubiquitin-positive) axonal spheroids in several brain regions after repeated injections (5 to 20 µg) of HGT-1410 into the CSF of MPS III mutant mice via the cisterna magna (ie, IT). The biochemical changes were accompanied by improved behavior, particularly in mice treated more frequently.[20]

In the MPS IIIA mutant mouse model, intracisternal (ie, IT) injection of a single dose of 100 µg HGT-1410 resulted in a substantial (and sustained) reduction of biomarkers of disease activity (heparan sulfate-derived disaccharides, microgliosis and astrogliosis).[21] Equally impressive was the improvement in neurobehavioral parameters (learning in the Morris water maze, normalization of aggression) in these mice post-dose.[21] One-hundred µg HGT-1410 per mouse translates into 200 mg/kg brain weight (ie, based on a 0.5 g mutant mouse brain). Efficacy at lower doses of HGT-1410 (eg, 20 µg, given IT, EOW or monthly) has been demonstrated.[11] A 20 µg injection translates into a 40 mg human dose (ie, 40 mg per kilogram of brain weight). Thus, this data further suggests that efficacy will be seen at the highest clinical dose (90 mg, per month) in the proposed Phase I/II study.

In the tolerized Huntaway (San A) dogs, 3 mg HGT-1410 was initially given IT on a weekly basis, then EOW, and had a significant effect on biomarkers of disease activity.[22] The 3 mg dose in the dog translates into a 33 mg (per kg brain weight) human dose (based on a 90 g Huntaway dog brain).

1.3 HGT-SAN-067 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 patients who completed Study HGT-SAN-055 and elected to continue therapy with HGT-1410.

Patients who were enrolled in Study HGT-SAN-055 through Week 26 and completed the end of study (EOS) evaluations are eligible for enrollment in this open-label extension study. All patients enrolled in this study will initially receive HGT-1410 at the same dose and schedule as

they received in Study HGT-SAN-055. Patients assigned to 10 mg monthly had their dose increased to 45 mg monthly once per month (Q4W) at the first administration of HGT-1410 following full approval of Protocol Amendment 4. Based on analyses performed at the completion of Study HGT-SAN-055 a decline in the primary pharmacodynamic parameter, CSF heparan sulfate, was observed. This response to therapy was exhibited at all dose levels, however, the greatest impact was at the 2 higher dose levels. An effect on CSF heparan sulfate demonstrated in vivo activity of HGT-1410 in the target anatomical compartment. This effect is thought to have central importance in mediating the potential therapeutic benefit of HGT-1410. As no apparent difference in safety profile was observed between the 3 dose groups, it was believed that the increase in the potential therapeutic benefit of the higher dose outweighed any potential increase in risks for this lowest dose group.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of HGT-1410 and PORT-A-CATH IDDD and SOPH-A-PORT Mini S device.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To collect long-term safety and tolerability data in patients 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.

2.2 Secondary Objectives

The secondary objectives of this study are:

- 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.

2.3 Exploratory Objective

An exploratory objective of this study is:

- [redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

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

- adverse events (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).

3.2 Secondary Endpoints

The secondary endpoints of this study are 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 and heparan sulfate derivatives in CSF and GAG, including heparan sulfate and heparan sulfate derivatives, in urine.
- Brain magnetic resonance imaging (MRI) and auditory brainstem response (ABR), (also known as Brainstem Auditory Evoked Potentials).

3.3 SOPH-A-PORT Mini S Assessments

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study HGT-SAN-067, is an open-label, long term, multicenter, extension of Study HGT-SAN-055. This study is designed to evaluate the long-term safety, clinical activity, and biomarker outcomes of IT administration of 3 dose levels (10 mg, 45 mg, and 90 mg once per month [Q4W]) of HGT-1410 via an IDDD in patients with MPS IIIA who successfully completed HGT-SAN-055 (including the EOS assessments) and elect to continue to receive uninterrupted HGT-1410 treatment. Patients will initially continue in the same treatment group they were assigned to in the HGT-SAN-055 study:

- 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)

Patients assigned to Group 1 will initially receive 10 mg monthly but had their dose increased to 45 mg monthly (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

Primarily main sites will be utilized; however, the sponsor and investigator will consider the feasibility of transitioning the patient's IT dosing to local sites to reduce the burden imposed by travel. At Month 18 (12 months after study start), patients that already received IT dosing at the main site may be eligible to transfer to a local site if in the opinion of the investigator there are no safety or medical concerns precluding this transition. Subsequent IT injections of HGT-4110 may be performed at either the main site or the local site. The local sites will be selected and approved by the sponsor, and the patient must have no safety or medical issues that would preclude transitioning to a local site (Note: the main site may serve as a local site as needed; and in this case, the main site will follow the assessments scheduled for a local site). The qualification requirements for physicians at local sites will be identical to those for the main sites. Local sites will be trained if inexperienced with IT administration via an IDDD. Patients will be discharged a minimum of 4 hours after dosing and when deemed clinically stable by the investigator. Dosing by IT injection may take place at the main site, rather than local site, if scheduled study assessments include MRI and cognitive assessments. Patients must review and agree to written informed consent/assent from the local site to participate in study procedures to be conducted at the local site prior to the conduct of these procedures.

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 patient received their first IT dose of HGT-1410 in Study HGT-SAN-055. The HGT-SAN-055 EOS assessment information will provide the screening/start of study information for patients who continue into the HGT-SAN-067 extension study. Note: HGT-SAN-055 EOS data must be recorded in the context of the HGT-SAN-055 trial, and a copy of those data can be used for HGT-SAN-067 screening. Once eligibility is confirmed, informed consent (and assent, if applicable), provided by the patient's parent(s)/legally authorized representative(s), must be obtained prior to performing any

HGT-SAN-067 study-related procedures. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

Enrolled patients will check 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 exist, the patient will subsequently receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the investigator.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067, during the treatment period, with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, such additional assessments may be added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out, during the treatment period of the study.

An MRI of the head will be performed at Months 12, 24, 36, 54, 60, 72, 84, 96, and 102 and ABR testing will be performed at Months 12, 24, 36 and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study), during the treatment period of the study.

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055).

Patients will be evaluated for safety throughout the study. Adverse events that occur in HGT-SAN-055 and are ongoing at enrollment in HGT-SAN-067 will be captured as ongoing in the HGT-SAN-055 study and also be reported as a concurrent condition in the HGT-SAN-067 eCRFs. Specific safety stopping criteria will be applied and will be based on the types and severity of AEs reported while on-study. These data will be reviewed to inform the decision to discontinue a patient, a dose group, or the study as a whole.

All patients will have an EOS visit during the treatment period, 30 (±7) days following their last administration of HGT-1410 (ie, Month 102). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child

health questionnaires, and MRI. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit, of the treatment period, (ie, Month 103) to collect updated information on AEs and concomitant medications, therapies, and procedures.

If the patient is discontinued from the study, the IDDD should be removed and a modified end of study visit should be completed within 30 days after withdrawal. These visits may be combined into one visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. If the investigator determines that the IDDD should not be removed from the patient based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit.

It is anticipated that the IDDD will be used to obtain CSF samples and to administer HGT-1410. However, if a patient's PORT-A-CATH IDDD appears nonfunctional or if its use is precluded on a scheduled day of dosing, site personnel will refer to the PORT-A-CATH Instructions for Use (IFU), which describes the investigation and management of IDDD-related issues with this device. This will include possible partial revision or complete replacement of the PORT-A-CATH IDDD with a SOPH-A-PORT IDDD. For malfunctions involving the SOPH-A-PORT Mini S, site personnel will refer to the SOPH-A-PORT IFU. For either IDDD, a maximum of 2 partial revisions and/or complete replacements are permitted in any 6 month period (including participation in study HGT-SAN-055). If a revision or replacement of the IDDD cannot be scheduled in time to avoid a delay of the next scheduled dose of HGT-1410, or if the patient experiences more than 2 IDDD malfunctions in a 6 month period, HGT-1410 will be administered via lumbar puncture (LP). If implantation of a replacement IDDD is not possible, investigational drug may be administered by LP for a maximum of 12 successive monthly doses. At that point, a safety discussion needs to take place between the investigator and the sponsor to determine the risk/benefit of further dosing by LP.

If there is no significant safety risk in the opinion of the investigator, a non-functional IDDD may be left in situ for up to 3 months during the treatment period.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If during the treatment period, a patient discontinues, or withdraws from the study, or the study is stopped by the sponsor, the IDDD should be removed unless the Investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

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.

An overview of the study appears in the Schedule of Events (Appendix 1). See Appendix 1, Table A1-2 for the Study Schedule of Events for the safety follow-up period for patients with partial or full devices in place after the end of the treatment period.

4.2 Rationale for Study Design and Control Group

The original study, Study HGT-SAN-055, is an ongoing Phase I/II safety and ascending dose ranging study of IT administration of HGT-1410 via an IDDD, in patients 3 years of age and older with MPS IIIA and early cognitive impairment. This extension study is proposed to continue evaluation of the effects of IT HGT-1410 administration on long-term safety and clinical outcomes for patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in the HGT-SAN-067 study.

In order to traverse the blood-brain barrier, Shire is evaluating HGT-1410 delivered directly to the CNS using an IDDD. The advantage of using an IDDD is that it obviates the need for multiple lumbar punctures for drug delivery. Drug products will be administered through this port or, if the IDDD is non functional, via lumbar puncture.

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

SOPH-A-PORT Mini S revision, implantation or explantation will be performed at the main site. However, if in the opinion of the investigator, emergency removal is clinically necessary, device explantation may be performed at the patient's local site.

4.3 Study Duration and Dates

The study duration allows patients who completed Study HGT-SAN-055 and elected to continue treatment with HGT-1410 in Study HGT-SAN-067 to receive treatment with HGT-1410 up to 8 years.

Patients with a partial or full device still in place after completion of the treatment period, may be followed for safety up to an additional 3 years or until the device is removed in the last patient.

The LPLV will be the safety follow-up visit after the final device (partial and/or full) is removed from the last patient during the safety follow-up period.

5 STUDY POPULATION SELECTION

5.1 Study Population

Patients who have completed all study requirements in Study-HGT-SAN-055 and who elected to continue HGT-1410 treatment will be eligible to participate; a maximum of 12 patients are planned for this study.

5.2 Inclusion Criteria

Each patient must meet the following criteria to be considered eligible for enrollment in this study.

1. The patient must have completed Study HGT-SAN-055 and, in the opinion of the investigator, have no safety or medical issues that contraindicate participation.
2. The patient, patient's parent(s) or legally authorized representative(s) has voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved informed consent (and assent, if applicable) form after all relevant aspects of the study have been explained and discussed with them. Informed consent/assent must be obtained prior to any study specific procedures.
3. The patient has received at least 5 of the 6 planned infusions of HGT-1410 in the HGT-SAN-055 study.
4. The patient must be medically stable, in the opinion of the investigator, to accommodate the protocol requirements, including travel, assessments, and IDDD surgery (if necessary for replacement purposes), without placing an undue burden on the patient/patient's family.

5.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following:

1. The patient has experienced an adverse reaction to study drug in Study HGT-SAN-055 that contraindicates further treatment with HGT-1410.
2. The patient has a known hypersensitivity to the active ingredient or any excipients in HGT-1410 drug product.
3. The patient has significant non-MPS IIIA related central nervous system impairment or behavioral disturbances that would confound the scientific integrity or interpretation of study assessments, as determined by the investigator.
4. The patient has MPS IIIA behavioral-related issues, as determined by the investigator, which would preclude performance of study neurocognitive and developmental testing procedures.
5. The patient is pregnant, breast feeding, or is of childbearing potential who will not or cannot comply with the use of an acceptable method of birth control, such as condoms, barrier method, oral contraception, etc.
6. The patient has any known or suspected hypersensitivity to anesthesia or is thought to have an unacceptably high risk for anesthesia due to airway compromise or other conditions.
7. The patient has a history of a poorly controlled seizure disorder.

8. The patient is currently receiving psychotropic or other medications, which in the investigator's opinion, would be likely to substantially confound test results and the dose and regimen of which cannot be kept constant throughout the study.
9. The patient cannot sustain absence of aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study-related procedure (eg, device re-implantation if applicable), or has ingested such medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
10. The patient has received treatment with any investigational drug (other than HGT-1410) intended as a treatment for MPS IIIA within the 30 days prior to, during the study, or is currently enrolled in another study that involves an investigational drug or device (screening through safety follow-up contact).
11. The patient has received a hematopoietic stem cell or bone marrow transplant.

For patients to be implanted with the SOPH-A-PORT Mini S IDDD the following conditions are contraindicated, as described in the Instructions for Use:

1. The patient has had, or may have, an allergic reaction to the materials of construction of the SOPH-A-PORT Mini S device.
2. The patient's body size is too small to support the size of the SOPH-A-PORT Mini S Access Port, as judged by the investigator .
3. The patient has a known or suspected local or general infection.
4. The patient is at risk of abnormal bleeding due to a medical condition or therapy.
5. The patient has one or more spinal abnormalities that could complicate safe implantation or fixation.
6. The patient has a functioning CSF shunt device.
7. The patient has shown an intolerance to an implanted device.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Intrathecal Drug Delivery Device

The PORT-A-CATH will continue to be used for the administration of drug product for each patient until such time as an IDDD replacement may be required. Following implementation of protocol Amendment 4, any replacements will be performed using the SOPH-A-PORT Mini S.

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

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

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

Further details are provided in the Instructions for Use.

6.1.3 Placebo or Control

This study will not employ a placebo or control.

6.2 Treatment Administered

HGT-1410 for IT administration will be provided by Shire. HGT-1410 will be administered by an IDDD. Following the review and signing of informed consent (and assent, if applicable), eligible patients will initially receive the same dose of HGT-1410 they received 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)

Patients assigned to Group 1 had their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

The study drug will be administered through an IDDD.

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

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

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

6.3 Selection and Timing of Dose for Each Patient

Patients will check into the study center 1 day prior to IT HGT-1410 dosing for safety assessments, designated Day 1, on each HGT-1410 treatment week, and if no safety concerns exist, will receive IT administration of HGT-1410 on Day 2 (±2 days). However, if feasible and there are no safety concerns in the opinion of the investigator, the Day 1 and Day 2 assessments and dosing may be combined and performed on Day 2; if this is done the results will be recorded as Day 2. Patients will remain in the study center for at least 4 hours following dosing with HGT-1410 and will be discharged from the unit when deemed clinically stable by the investigator.

The IT injections are to be administered every 28 days (±7 days). If a patient's IDDD becomes nonfunctional, it may be revised (partial or complete) (a maximum of twice in a 6 month period) so that the patient can remain on study (see Section 7.12 for details).

6.3.1 Cerebral Spinal Fluid Sample Procedure

CSF samples will be obtained prior to each injection for clinical laboratory evaluation and potential biomarker studies. The IDDD will be used for CSF sampling and a topical anesthetic agent may be applied over the skin covering the IDDD reservoir prior to sampling. Site personnel should refer to the operations manual for instructions on the use of topical anesthesia prior to accessing the IDDD reservoir.

If use of the IDDD is precluded on a scheduled day of dosing, CSF samples may be obtained by LP, as described in the IDDD Manual and Section 6.3.2. Intrathecal Administration of HGT-1410.

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered using an IDDD. After appropriate pre-procedure assessments are completed, anesthesia cream will be applied to the skin over the port. Patients may receive sedation as necessary to alleviate anxiety and/or to facilitate drug delivery.

Patients will receive HGT-1410 via slow push/injection through an appropriately sized syringe (see the Pharmacy Manual). Replacement of fluid, including drug, to the CSF will be an approximate equal volume to that removed. The patient's vital signs will be continuously monitored. The patient will also be monitored closely during study drug administration and through the next 4 hours for any adverse clinical reactions. The patient will be encouraged to lie down comfortably for 1 to 3 hours post injection, although this may be difficult for the most hyperactive patients.

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

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

In the event of IDDD malfunction, CSF collection and study drug administration may be performed via LP (see Section 6.3.2). The investigation and management of a malfunctioning IDDD is detailed in the PORT-A-CATH or SOPH-A-PORT IFUs. Partial or complete replacement of the IDDD may be necessary (only permitted twice in a 6-month period, including the time a patient was in study HGT-SAN-055), and will require scheduling of the appropriate procedure. The definitive diagnosis of the cause of IDDD failure may not be possible until the time of exploratory surgery. Surgery will take place at the earliest convenience, so the patient may remain on, or as close as possible to their treatment schedule.

6.3.2 Administration of HGT-1410 via Lumbar Puncture Guidance Concerning Performance of Lumbar Puncture for Study Drug Administration and Cerebrospinal Fluid Sample Collection

It is intended that the IDDD will be used to deliver all IT injections of study drug and to obtain CSF samples. If the IDDD appears to be nonfunctional, or if its use is precluded on a scheduled day of dosing, site personnel will refer to the IDDD manual (s), which provides details on the investigation and management of any IDDD-related issues. This may include possible partial revision or complete replacement of the IDDD as indicated. If the nonfunctional IDDD is a PORT-A-CATH device, then it will be replaced by a SOPH-A-PORT Mini S device.

If there are medical contra-indication to the re-implantation of a new device, or if the patient so desires, repeat monthly lumbar punctures may be considered as an alternative way of delivering

the study drug and obtaining CSF samples under limited circumstances. If no safety risks are identified by the investigator, up to 12 consecutive lumbar punctures may be performed across studies HGT-SAN-055 and HGT-SAN-067. Once a patient has reached the maximum of 12 consecutive lumbar punctures, a new IDDD will be re-implanted for subsequent dosing, unless, in the opinion of the investigator and medical monitor, assessment of risk/benefit favors continued dosing via lumbar puncture.

Continued treatment via repeat lumbar puncture beyond the stipulated 12 consecutive monthly doses can be considered only in individual cases of patients where this treatment is very well tolerated and the investigator has not identified any safety concerns associated with repeat lumbar puncture and repeat sedation/anesthesia.

6.4 Method of Assigning Patients to Treatment Groups

This is an open-label, non-randomized study; all patients enrolled in this study will be treated with HGT-1410. Patients will initially receive the same dose of HGT-1410 they received in Study HGT-SAN-055. Patients assigned to Group 1 (10 mg once per month [Q4W]) had their dose increased to 45 mg once per month (Q4W) at the first administration of HGT-1410 following full approval of protocol Amendment 4.

6.5 Blinding

Not applicable; as this trial is not blinded.

6.6 Concomitant Therapy

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

Every effort should be made to keep the patient's symptomatic Sanfilippo syndrome Type A 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 World Health Organization Drug Dictionary (WHO-DD).

6.7 Restrictions

6.7.1 Prior Therapy

Prior therapy excluded for this study consists of the following:

- Psychotropic or other medications, which in the investigator's opinion would be likely to substantially confound test results, and the dose and regimen of which cannot be kept constant throughout the study.

- The patient cannot sustain absence from aspirin, non-steroidal medications, or medications that affect blood clotting within 1 week prior to a relevant study related procedure (eg, device implantation if applicable) or medications within 1 week before any procedures in which any change in clotting activity would be deleterious.
- The patient has received any investigational drug or device intended as a treatment for MPS IIIA within the 30 days prior to the study other than HGT-1410 or is enrolled in another study that involves an investigational drug or device.
- Hematopoietic stem cell or bone marrow transplant.

6.7.2 Fluid and Food Intake

Food and fluid intake are not restricted over the course of the study, with the exception of hospital standard pre-anesthesia dietary restrictions.

6.7.3 Patient Activity Restrictions

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

6.8 Treatment Compliance

HGT-1410 is administered under controlled conditions by the investigator; therefore, full patient compliance with study treatment is anticipated in this study.

6.9 Packaging and Labeling

6.9.1 Drug Product

Drug product will be supplied in a 3 mL clear, colorless glass (Type 1) vial. Each vial holds an extractable volume of 1 mL of HGT-1410. The closure is a gray, 13 mm stopper composed of butyl rubber with a fluoro resin lamination. The overseal is an aluminium seal with a flip-off, plastic, tamper evident cap.

See the Pharmacy Manual for additional details.

6.9.2 SOPH-A-PORT Mini S Access Port

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

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

6.10 Storage and Accountability

6.10.1 Investigational Product

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

All HGT-1410 study drug delivered to an investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the sponsor or its designee or disposed of after sponsor approval per site policy after study completion.

6.10.2 Intrathecal Drug Delivery Device

6.10.2.1 PORT-A-CATH IDDD

Please refer to the operations manual for return instructions.

6.10.2.2 SOPH-A-PORT Mini S IDDD

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

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

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

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

6.11 Investigational Product Retention at Study Site

All HGT-1410 study drug delivered to an investigator will be recorded and accounted for throughout the study. All HGT-1410 study drug must be recorded on a patient-by-patient basis. The lot number of the IDDD and the date and time of administration of the study medication will be documented on the appropriate eCRF.

All unused study medication and other study materials are to be returned to the sponsor or its designee or disposed of after sponsor approval per site policy after study completion.

7 STUDY PROCEDURES

7.1 Informed Consent

Study procedures will be conducted only after written informed consent for the patient to participate in this study is provided by the parent(s) or the patient's legally authorized representative(s) and assent from the patient (if applicable). Detailed descriptions of patient evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of each study month (see Appendix 1, Table A1-1 and A1-2 Schedule of Events).

All data collected are to be recorded on the appropriate eCRF. Blood, urine and CSF volumes to be collected for each clinical laboratory measurement are described in detail in the Laboratory Manual.

After the treatment period ends, informed consent from patients who do not have the IDDD removed (partial or full device) will be obtained for the safety follow-up period.

7.2 Physical Examination

A full physical examination or a symptom-directed physical examination of each patient will be performed at time points detailed in Appendix 1, Table A1-1 Schedule of Events, for the duration of the treatment period. The physical examinations for the safety follow-up period will be symptom-directed, see Appendix 1, Table A1-2 Schedule of Events, for details.

Any changes from the screening physical examination will be captured as AEs in the eCRF. If the patient experiences an AE associated with genitourinary evaluation, the patient may have the genitourinary evaluation performed by their primary care provider and a follow-up report will be sent to the investigator. Therefore, the genitourinary evaluation may not need to be performed again if the examination occurred within the visit window for that time point.

Note: if the patient's hearing cannot be assessed during the physical examination, the patient will have an Ears, Nose, and Throat Evaluation performed under anesthesia at the screening/start of study visit. If it is determined that the patient requires pressure-equalization (PE) tubes, they may be implanted during that evaluation (see Section 7.9). Note: PE tubes may be re-implanted if they fall out during this study.

The physical examination findings will be recorded on the eCRF and will include a review of the patient's general appearance as well as the following evaluations:

- Head and neck
- Eyes, ears, nose, and throat
- Chest and lungs
- Cardiovascular
- Abdomen
- Skin
- Lymphatic
- Musculoskeletal
- Neurological (symptom directed and at least every 12 months)
- Endocrine
- Genitourinary (as per referring physician)

7.3 Height and Weight

Height or length (cm), and weight (kg) will be measured once and recorded on the eCRF.

7.4 Head Circumference

Head circumference (cm) will be measured and recorded on the eCRF.

7.5 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements) will be measured and recorded on the eCRF.

7.6 Electrocardiography

7.6.1 Electrocardiograms

An ECG will be performed. Each ECG will include an assessment of heart rate, sinus rhythm, atrial or ventricular hypertrophy, PR, QRS, QT, and QTc intervals. The ECGs will be conducted in accordance with the clinical site's standard practice(s), and will be read locally at the clinical site. Identification of any clinically significant findings and/or conduction abnormalities will be recorded on the eCRF.

7.7 Clinical Laboratory Tests

Blood, urine, and CSF samples will be collected as described below for clinical laboratory testing. Procedures for collection and handling of samples are included in the Laboratory Manual. The conduct of a clinical trial in an extremely rare disease such as MPS IIIA provides a unique opportunity to collect samples for potential biomarker research. In the context of this study, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of the MPS IIIA pathogenic process, or a pharmacologic response to experimental therapy with HGT-1410. In addition to exploration of potential biomarkers, as part of the assessment of the SOPH-A-PORT Mini S, it may be necessary to determine the levels of leachables from the device into the CSF and blood.

For patients who do not have the IDDD removed (partial or full device) at the end of the treatment period, clinical laboratory testing will only be performed when indicated for a device-related AE during the safety follow-up period.

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, serum chemistry, and urinalysis.

Laboratory Parameters

Clinical laboratory tests will be performed at a central laboratory. Clinical laboratory tests will include the following:

7.7.1 Hematology

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

7.7.2 Serum Chemistry

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

In addition a leukocyte pellet will be prepared, stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (CRIM).

7.7.3 Pregnancy Test

A pregnancy test will be performed on Day 1 of each dosing week. Pregnancy testing will be performed using either a serum or urine sample (at the discretion of the site), and only on females who have reached menarche. All pregnancy testing and the reporting of results will be performed locally by the clinical site staff. Study drug must not be administered in the event of a positive or inconclusive pregnancy result.

7.7.4 Serum Anti-rhHNS Antibody and Sample Storage

Blood samples will be collected and evaluated at Shire or Shire-designated laboratories for the determination of anti-rhHNS antibodies. Samples will be reserved in accordance with local regulations for potential future MPS IIIA research that may determine biomarkers of disease severity and progression.

Two blood samples will be collected from each patient at each designated time point. One sample will be collected in tubes intended for serum specimens, while the second sample will be collected in tubes intended for plasma specimens. Blood sample collection, processing, and shipping instructions will be provided in the Laboratory Manual.

7.7.5 Urinalysis

Patient catheterization may be required for obtaining urine samples (if deemed necessary by the investigator).

7.7.5.1 Standard Urinalysis

The following urinalysis parameters will be performed at a central laboratory: pH, macroscopic and microscopic evaluations.

7.7.5.2 Urine Glycosaminoglycans

A urine sample will be collected for the determination of GAG (including heparan sulfate and heparan sulfate derivatives) and the analysis will be performed at Shire, or Shire designated laboratories. A urine sample from each visit will be reserved for possible exploratory biomarker studies that may provide new indicators or markers of MPS IIIA disease severity or progression.

7.7.6 Cerebrospinal Fluid Assessments

Cerebrospinal fluid sample collection, processing, and shipping instructions will be provided in the Laboratory Manual. A CSF sample will be reserved for possible exploratory biomarker studies for MPS IIIA disease.

Each CSF sample collected will be assessed for appearance and will be analyzed using the assays listed in Sections 7.7.6.1, 7.7.6.2, and 7.7.6.4. In addition, as more is learned about Sanfilippo CNS pathology and etiology, future exploratory assays of CSF metabolites, protein or ribonucleic acid (RNA) may become used as they become available in the future.

7.7.6.1 Cerebrospinal Fluid Cell Counts

An aliquot of each CSF sample collected will be evaluated for CSF standard chemistries, glucose, protein, and cell counts. These assessments will be performed at the local laboratory.

7.7.6.2 Cerebrospinal Fluid Heparan Sulfate Levels and Heparan Sulfate Derivatives

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of CSF heparan sulfate and heparan sulfate derivatives at Shire designated laboratories.

7.7.6.3 Anti-rhHNS Antibodies

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of anti-rhHNS antibodies at Shire or Shire designated laboratories.

7.7.6.4 Cerebrospinal Fluid Biomarkers

An aliquot of each CSF sample collected will be quick frozen as per the Laboratory Manual for subsequent determination of MPS exploratory biomarkers at Shire or Shire-designated laboratories.

7.7.7 Sample Collection, Storage, and Shipping

Sample collection, processing, and shipping instructions will be provided in the Laboratory Manual to be provided by Shire.

CSF, urine, and serum samples may be reserved for potential, future, biomarker studies. Samples will be stored securely to ensure patient confidentiality.

7.8 Anesthesia

Administration of anesthesia/sedation will be given prior to obtaining CSF (when the use of the IDDD is precluded), prior to performing a MRI of the head, the ABR, the CSF opening pressure, and the partial revision or replacement of the IDDD (if applicable).

See Appendix 1 for the Schedule of Events. When logistically feasible, the MRI, ABR, and surgical implantation of the IDDD may be performed together to reduce exposure to general anesthesia.

Note: The neurologic exam and the neurocognitive and developmental assessments must be performed prior to the administration of anesthesia.

7.9 Audiometry and Auditory Brainstem Response

The rare attenuated patients with MPS IIIA with high levels of cognitive functioning will have hearing tests via clinical audiometry measurement performed using age-appropriate testing methods based on the child's developmental age at the time of the testing. It is anticipated that most of the cognitively-impaired and/or behaviorally-deteriorated patients with Sanfilippo A will be unable to cooperate with a (conscious) hearing evaluation. In these instances, the investigator will utilize his best clinical judgment to estimate the extent of hearing loss (if any) during the physical examination. In this situation, a specific evaluation of hearing loss will occur during an examination of waveforms in the ABR (see below). If the patient has a history of multiple instances of otitis media or evidence of clinically-significant otitis media on physical examination, which the investigator believes causes significant conductive hearing loss and impairment of daily living, the investigator will discuss and offer the parent or legally authorized representative(s) placement of PE tubes as part of the scheduled anesthesia. A patient's PE tubes may be replaced if they fall out during the course of this study.

The ABR will be conducted under anesthesia. The ABR findings will be considered within normal limits if, after applying appropriate correction factors, the waveforms reveal normal morphology.

7.10 Magnetic Resonance Imaging of the Head

The regional brain volume will be assessed through a MRI, of the head. The patient will be under general anesthesia for this assessment. All MRIs will be centrally read by the University of Minnesota Medical Center. Refer to the Study Operations Manual for specific procedures and precautions.

7.11 Device Data

7.12 Surgical Re-implantation of the IDDD

If a patient's IDDD becomes nonfunctional or infected, it will be replaced or revised so that the patient can remain on study. After full approval of protocol Amendment 4, all IDDD replacements will be made with the SOPH-A-PORT IDDD. If the IDDD device is a PORT-A-CATH IDDD, it will be replaced by a SOPH-A PORT IDDD. Management details for the PORT-A- CATH IDDD or for the SOPH-A PORT IDDD are provided in the respective device's IFU. Procedures for implantation are detailed in the relevant device's Instructions for Use Manual and in the training materials provided by Shire. The patient will be under general anesthesia for this procedure. Standard hospital procedure for surgery will be followed and will include an X-ray to confirm that the device has been (1) surgically implanted correctly, and (2) positioned so that the intrathecal catheter tip is at the mid-thoracic level (a check list is provided in the IDDD Manual).

A post-operative check of the IDDD and incision will be performed on Day 4 following surgery. X-rays may be performed to check placement of the device, as needed, throughout the study (see Section 7.12.1 for limits on the number of x-rays and IDDD revisions and or replacement).

7.12.1 Restrictions on the Number of Revision and/or re-implantation of the IDDD

A non-functional IDDD can be replaced or revised twice in a 6-month period, including the time a patient was in study HGT-SAN-055. Similarly, 6 X-rays may be taken in a 6-month period (including the time in HGT-SAN-055).

7.13 Device Related Study Procedures

7.13.1 IDDD Implantation or Revision Procedures

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

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

Details of the implantation/revision and malfunctions/failure for the SOPH-A-PORT will be documented on the patient's eCRF.

7.13.2 X-ray Verification of Intrathecal Drug Delivery Device Placement

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

7.13.3 CSF Sampling Procedure

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

7.13.4 Device Removal

If at the time of a scheduled dosing it is not possible to administer a full medication dosage as per the standard administration steps detailed in the device's IFU due to a device-related issue, the IDDD will be declared a device malfunction. If the device malfunction is irreversible and cannot be corrected without a device surgical intervention, the IDDD will be declared a device failure, starting from the date of the initial malfunction.

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

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

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

If the IT space is not accessible via the IDDD, study drug may be administered by LP up to 5 times.

Patients should have the IDDD removed when they discontinue from the treatment period of the study, unless the Investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

7.14 Cerebrospinal Fluid Opening Pressure Measurement

A CSF opening pressure measurement (cm of H_2O) will be conducted as per standard hospital practice. The measurement will be obtained whenever a LP is performed and an IDDD revision or replacement is done. Following implementation of Amendment 6 the CSF opening pressure measurement will not be required with the LP.

7.15 Dispensing Study Drug

A visual examination of both the port and catheter track will be performed before each IT injection.

HGT-1410 will be administered IT by means of an IDDD (or via LP if necessary) to patients on Day 2 (±2 days) of Week 1 of each treatment month.

The patient may be sedated for this procedure. HGT-1410 will be administered through an appropriately sized syringe (see the Pharmacy Manual). If the IT space is not accessible via the IDDD, HGT-1410 may be administered via LP. See Section 6.3.2 for details.

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

7.16 Pharmacokinetic Assessments

Pharmacokinetic assessments are not included in this study.

7.17 Neurological Examination

A neurological examination to monitor CNS changes in a patient's neurological status will be conducted during this study. See Appendix 2 for a complete list of the neurological examinations.

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

7.18 Neurocognitive and Developmental Assessments

Patients will undergo neurocognitive and neurobehavioral development testing. The assessments are estimated to last between 2 and 4 hours and must be conducted prior to sedation or anesthesia.

A full neurodevelopmental assessment, including global development, cognition, adaptive behavior, receptive and expressive language, and gross motor function, will be evaluated using standardized developmental and behavioral tests to provide a surrogate and quantifiable measure of global CNS neurodevelopmental/neurobehavioral function.

All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, patients in HGT-SAN-067 will continue with the age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing assessments at a higher level, any such additional assessments may be added. Any additional assessments would be performed after the original assessments have been carried out.

For this study, outcome measures will be computed for each patient enrolled. The psychometric instruments and Sanfilippo-specific assessments are summarized below in Table 7-1 and Table 7-2, respectively. See Appendix 2 for details on these assessments.

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
COGNITIVE DEVELOPMENT ASSESSMENT	
Summary score and sub-domains: - Cognitive - Motor - Social/emotional	0 to 42 months: Bayley Scales of Infant Development-III Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years: Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]

Table 7-1 Neurodevelopmental Assessments Tests

Developmental or Cognitive Domain(s)	Patient Age: Representative Cognitive Test or Scale
GROSS AND FINE MOTOR SKILLS ASSESSMENT AND VOLUNTARY MOVEMENT	
Motor	3.0 to 16:11 years: Movement Assessment Battery for Children II (MABC-2)[25]
- Cognitive - Motor	0 to 5 ½ years: Bayley Scales of Infant Development III (BSID-III)[23]
ADAPTIVE BEHAVIOR	
Communication Daily Living Socialization Motor Skills	0 to 90 years: Vineland Adaptive Behavior Scales (VABS-II) Second Edition[26]

Table 7-2 Sanfilippo-Specific Disability Assessment And Behavior Rating Scales

DEVELOPMENTAL OR COGNITIVE DOMAIN(S)	SANFILIPPO SPECIFIC ASSESSMENTS
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale (SBRS)
MPS-specific disability score - cognitive functioning - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

7.19 Sleep Questionnaire: Children's Sleep Habits Rating Scale

A sleep questionnaire, Children's Sleep Habits Rating Scale, will be administered to the patient's parent(s)/legally authorized representative(s).

7.20 Age-Dependent, Health-Related Quality of Life in Children

The Quality of Life questionnaires will be administered as outlined in Sections 7.20.1, 7.20.2, and 7.20.3.

7.20.1 Quality of Life Indicator: CHQ-50

The Child Health Questionnaire™ Parent Form 50 Questions (CHQ-50) will be administered during the study. The questionnaire is a generic quality of life instrument, measuring 14 unique physical and psychosocial concepts, which was developed for children from 5 to 18 years of age.

7.20.2 Quality of Life Indicator: CHQ-87

The Child Health Questionnaire™ Child Form 87 (CHQ-87) will be administered during the study. The CHQ-87 is a child and adolescent self-report, developed for ages 10 and older, which assesses the child's self-perceived physical and psychosocial well-being.

7.20.3 Quality of Life Indicator: ITQOL

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) will be administered during the study. The ITQOL was developed for children at least 2 months of age up to 5 years and assesses the physical, mental, and social well being of the child and assesses the quality of the parent/legally authorized representative(s) life.

7.21 Concomitant Medications, Therapies and Medical/Surgical Procedures

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

Every effort should be made to keep symptomatic Sanfilippo syndrome Type A 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 WHO-DD.

7.22 Adverse Events

7.22.1 Definitions of Adverse Events and Serious Adverse Events

7.22.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered study drug-related. This includes an exacerbation of a pre-existing condition. Once the informed consent is signed and dated, any adverse event prior to the start of study drug must be reported.

AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions

- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight

Throughout the study, the investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to study drug. The investigator should treat patients with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. AEs may be discovered through observation or examination of the patient, questioning of the patient, complaint by the patient, or by abnormal clinical laboratory values.

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

All AEs should be recorded with causality assessment.

The information presented below is intended to provide issues to consider for AEs associated with intrathecal injections of HGT-1410. In general, these AEs can be classified as follows:

- Adverse events due to systemic exposure to HGT-1410 caused by the drug diffusion from the CSF to the peripheral circulation;
- Adverse events related to the direct delivery of HGT-1410 to the intrathecal CSF space and meninges, and subsequent diffusion into brain parenchyma, via an intrathecal route
- IDDD–related AEs

Note: the classification of potential AEs and the examples presented below are based on purely theoretical considerations and/or published literature as there is limited human experience with intrathecal HGT-1410 therapy to date.

7.22.1.2 Potential Adverse Events: Intrathecal recombinant human heparan N-sulfatase

ADVERSE EVENTS RELATED TO THE DIRECT DELIVERY OF HGT-1410 TO THE CNS THROUGH INTRATHECAL ADMINISTRATION

Examples of AEs observed in other published clinical trials with intrathecally-administered peptides or proteins, include, but are not limited to the following: headache, fever, feeling of warmth, sensory paresthesias (including feelings of warmth, tingling, or pain) or autonomic symptoms such as dry mouth or gustatory abnormalities (including loss of smell and metallic taste). Changes in mental cognitive status or level of consciousness that are not caused by pre-medication may either occur acutely or develop post-injection, over time.

ADVERSE EVENTS DUE TO SYSTEMIC EXPOSURE TO HGT-1410

Although HGT-1410 is given intrathecally only, some proportion of the drug will diffuse from the CSF into the peripheral circulation. The resulting systemic exposure may cause events that

are typically seen in patients receiving ERT via an intravenous administration, known as infusion-related reactions. An infusion-related reaction is defined as an adverse event that (1) begins either during or within 24 hours after the start of the infusion, and (2) is judged as possibly or probably related to study drug. Other AEs that occur prior to the infusion, along with AEs associated with protocol-defined testing and assessments (laboratory testing and physical examinations) that were performed prior to the infusion will not be defined as infusion-related reactions.

7.22.1.3 Infusion/Hypersensitivity Reactions and Management

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

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

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

7.22.1.4 IDDD-related Adverse Events

IDDD ADVERSE EVENTS

Examples of AEs related to use of the IDDD include, but are not limited to, the following: device failure, device malfunction, incorrect connection of IDDD components, erosion of the portal/catheter through the skin, fibrin sheath formation around the catheter tip, hematoma, implant rejection, migration of the portal/catheter, occlusion of the portal/catheter, portal site, or subcutaneous tract infection. The device may also need to be replaced or repaired as needed. A malfunction of the device (defined in Section 7.22.2.2) should not be entered as an AE unless it has physiological consequences. In the event of a device failure (defined in Section 7.22.2.3), the device may need to be replaced or repaired. Hospitalization for such a procedure will be reported as a serious adverse event (SAE). Details of the cause of IDDD malfunction or failure will be recorded on the Device Malfunction/Failure CRF. A list of the more common IDDD AEs is included in Appendix 3.

DEVICE SURGICAL PROCEDURE-RELATED ADVERSE EVENTS

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

IT ADMINISTRATION PROCESS ADVERSE EVENTS

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

RISKS ASSOCIATED WITH ANESTHESIA REQUIRED FOR STUDY ASSESSMENTS

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

RISKS ASSOCIATED WITH LUMBAR PUNCTURE

Risks associated with LP include pain at the injection site, infection, meningitis, encephalitis, cerebritis, failed procedure, bleeding, dural tears, spinal headache, spinal fluid leakage, nerve damage, and focal and non-focal neurological injury (including paralysis). Patients may require anesthesia prior to an LP. Risks from anesthesia are discussed separately in this section (Section 7.22.1.4).

7.22.1.5 Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization. Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s). *Furthermore, this does not apply to device failures resulting in scheduled surgical revisions, which should be reported as SAEs."*

2. Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients. (21CFR812.3[s] or other regulatory requirements, as applicable).

7.22.2 Device-Associated Definitions

7.22.2.1 Device Revision (Partial and Full)

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

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

7.22.2.2 Device Malfunction

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

7.22.2.3 Device Failure

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

7.22.2.4 Device Adjustment

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

7.22.3 Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 grading scale should be referenced when assessing the severity of an AE (see Appendix 6). If an AE is not described in the NCI CTC, the severity should be recorded based on the scale provided in Table 7-3. The severity of all AEs/SAEs should be recorded on the

appropriate eCRF page. Adverse events are graded as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or death.

Table 7-3 Adverse Event Severity

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

7.22.4 Relatedness of Adverse Events and Serious Adverse Events

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

Table 7-4 Adverse Event Relatedness

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

7.22.5 Procedures for Recording and Reporting Adverse Events

7.22.5.1 Reporting Serious Adverse Events Related to Study Procedures

Any SAE regardless of relationship to investigational product, device, device surgical procedure, or IT administration process that occurs in a patient after informed consent (and assent if applicable) should be recorded by the clinical site on an SAE form that is to be transmitted to the Shire Medical Monitor and to the Shire Pharmacovigilance and Risk Management Department at the contact number provided below. The SAE must be completely described on the patient's eCRF, including the judgment of the investigator as to the relationship of the SAE to the investigational product and or device. The investigator will promptly supply all information identified and requested by the sponsor (and/or contract research organization [CRO]) regarding the SAE as to the relationship of the SAE to study drug, device, or procedure.

The investigator must report the SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. The SAE form must be completed and FAXED or scanned and EMAILED (PDF sent by e-mail) within 24 hours of the investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:
International FAX: [redacted] **United Kingdom OR**
United States FAX: [redacted]
Email: [redacted]
AND
Shire HGT Medical Monitor:
FAX: [redacted] **(United States)**

The investigator may also call the medical monitor directly (optional):

Shire HGT Medical Monitor: [redacted] **DO**
[redacted]
Shire HGT
Work: [redacted]
Cell: [redacted] **(24 hour access)**
Email: [redacted]
AND
Clinical Project Manager CC'd: [redacted]

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

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone; this is in addition to completing and

transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

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

The investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the sponsor to ensure that each investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The investigator or sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files. In addition, the sponsor will also notify the investigators and IRBs/IECs of all deaths that occur during the study, irrespective of relationship to study medication.

7.22.5.2 Eliciting Adverse Events

Patients should be asked non-leading questions (eg, "How do you feel?") and further questions should be posed if there is indication of an AE. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information regarding AEs from questioning the patient, the patient's parent/guardian, spontaneous report by the patient or parent/guardian, laboratory reports, and any health care provider's observations.

The onset date, resolution date, treatment administered, and outcome of each AE must be recorded on the appropriate eCRF. The relationship of each AE to study medication must be recorded. In addition AEs may be considered to be related to the IDDD, the IDDD surgical procedure, or the IT administration process. Since the AE may be deemed to be related to more than one of these factors, as many of these IDDD-related options as apply should be indicated on the eCRF.

7.22.5.3 Protocol Deviations for Medical Emergency or Adverse Event

During and following a patient's participation in the study, the investigator should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory test results.

The investigator should inform the patient, the patient's parent(s), or the patient's legally authorized representative when medical care is needed for intercurrent illness(es) of which the

investigator becomes aware. In an emergency situation, the investigator should contact the Shire Medical Monitor (see Section 7.22.5.1).

Only when an emergency occurs that requires an immediate deviation from the protocol for the safety of a patient, will there be such a deviation and this will be only for that patient.

The investigator or other physician in attendance in such an emergency must contact the Shire Medical Monitor as soon as possible.

The investigator, along with the Shire Medical Monitor, will make a decision as to whether or not the patient should continue in the study prior to the next scheduled dose. The departure from the protocol and the grounds for it should be stated in the eCRF.

7.23 Abuse, Overdose and Medication Errors

Abuse, misuse, overdose or medication error must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 7.22.

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness)
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: This includes a situation where the test article is not used as directed at the dose prescribed by the protocol.)
- **Overdose –** Overdosage with adverse clinical consequences is not anticipated with the use of HGT-1410. Additionally, HGT-1410 will be given in a clinical setting by a health care provider.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

7.24 Safety-related Study Stopping Rules

If any patient experiences a life-threatening (Grade 4) adverse event or death which is considered by the sponsor to be possibly, probably, or definitely related to study drug **or the IDDD**, or if 2 or more patients experience a Grade 3 adverse event during the trial that is considered by the sponsor to be possibly, probably, or definitely related to the study drug **or the IDDD**, then the site will be instructed to halt further HGT-1410 administration to all patients and the safety data reviewed. Following a review of safety data, the study will be either:

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

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

7.25 Pregnancy

Pregnancy and breast feeding are exclusion criteria. Only female patients who have reached menarche will be tested for pregnancy in HGT-SAN-067. If applicable, this will occur at study start and before each dose of HGT-1410 throughout the study. Pregnancy testing will be performed on a blood or urine sample. Patients with a positive or inconclusive result will not be eligible for this study.

At study start, a pregnancy test will be performed if more than 30 days have passed since the initial screening sample. Throughout the study pregnancy testing will occur prior to each dose of HGT-1410. The clinical site's local laboratory will analyze and report all pregnancy testing results. If a pregnancy test is positive the patient will be discontinued from the study, and the investigator must contact the Shire Medical Monitor.

Pregnancy is not to be reported as an AE; the Pregnancy Reporting Form, found in the Study Operations Manual along with instructions for completion, should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.26 Removal of Patients from the Trial or Study Drug

The patient's parent or legally authorized representative acting on behalf of the patient is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. Since this is an extension trial, there will be no replacement of patients who discontinue the study for any reason.

A patient's participation in the study may be discontinued at any time at the discretion of the investigator, sponsor, or medical monitor. The following may be justifiable reasons for the investigator, sponsor, or medical monitor to remove a patient from the study:

- Adverse Event: If a patient experiences an AE which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient.
- Adverse Laboratory Experience: If a patient has an adverse laboratory experience which, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the patient, the patient may be withdrawn from the study.
- Comorbidity: If a patient develops comorbidity during the course of the study that is independent of the study indication, and treatment is required that is not consistent with protocol requirements.
- Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements.
- Refusal of Treatment: If the patient, the patient's parent(s) or legally authorized representative(s) discontinues participation in the study, or the patient is discontinued by the investigator, reasonable efforts will be made to follow the patient through the end of study assessments. The reason for refusal will be documented on the eCRF.

- Withdrawal of Informed Consent: A patient's parent or legally authorized representative may withdraw his informed consent to participate in the study at any time.
- Cerebrospinal fluid leukocyte count >100 cells per cubic millimeter for 2 consecutive months.
- New onset seizure.
- Anaphylactic reaction beyond reasonable management as described in the Investigator's Brochure.
- Clinically problematic intubations or extubations, which may preclude safe airway management and anesthesia.
- Development of refractory spinal fluid leakage.
- Clinically significant prolonged (eg, greater than 24 to 48 hours) worsening in mental status, including development of new focal or non-focal neurological symptoms, or recurrence of a previously stable prior medical problem judged due to study drug or participation that is exclusive of effects from anesthesia.
- Non-compliance, including failure to appear at 1 or more study visits.
- The patient was erroneously included in the study.
- The patient develops an exclusion criterion.
- The study is terminated by the sponsor.
- The patient becomes pregnant during the trial.

If a patient discontinues the study the Patient Completion/Discontinuation eCRF describing the reason for discontinuation must be completed. Any AE's experienced up to the point of discontinuation must be documented on the AE eCRF.

If AEs are present when the patient withdraws from the study, the patient will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit for the treatment period of the study. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient should be scheduled for the removal of the IDDD. The final evaluation in the safety follow-up period for patients who do not have the IDDD removed (full or partial device) is defined as the follow-up evaluation performed for up to 3 years after the treatment period ends.

7.27 Study Discontinuation Process

If the patient is discontinued from the study, the IDDD should be removed and a modified end of study visit should be completed within 30 days after withdrawal. These visits may be combined into one visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. The end of study visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution.

If the investigator determines that the IDDD should not be removed from the patient based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit. This last treatment period visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution. Once the patient completes their last treatment period visit, they will return for their first safety follow up visit in six months. The patient will continue in the safety follow-up period with a clinic visit every 6 months for up to 3 years or until the device is removed in the last patient. An end of study follow-up via a phone call should be completed within 14 days after the device removal to collect safety information (refer to Section 8.5).

7.28 Other Study Procedures

This section is not applicable.

7.29 Appropriateness of Measurements

The neurocognitive and developmental assessments are intended to gauge which domains can be accurately measured, with which specific tools, despite the considerable behavioral and cognitive challenges in Sanfilippo syndrome. The evaluation of these domains and the analysis of CSF, serum, and urine biomarkers may provide the pivotal data necessary to inform the clinical assessments and biomarkers used in possible future Sanfilippo syndrome ERT trials.

8 STUDY ACTIVITIES

Patients who participated in Study HGT-SAN-055 through Week 26 and completed the EOS evaluations may be eligible for enrollment in this open-label extension study. Informed consent (and assent, if applicable) must be obtained prior to performing any study related procedures that are specific to HGT-SAN-067. Informed consent may be obtained anytime from Week 20 in HGT-SAN-055. This would allow a patient to have a nonfunctional IDDD replaced or revised prior to the first HGT-1410 dose in HGT-SAN-067.

8.1 Screening Visit/Study Start Visit – Main Site

All Screening assessments for this study are to have been performed during the Week 26 EOS procedures in HGT-SAN-055 (ie, 30 [±7] days after the last HGT-1410 administration). If less than 60 days have elapsed since completion of the EOS assessments for HGT-SAN-055, and the start of HGT-SAN-067, the assessments detailed in this Screening visit do not need to be repeated. The Baseline visit for this study will be the first day the patient received their first dose of HGT-1410 in the HGT-SAN-055 Study.

If more than 60 days have elapsed following the HGT-SAN-055 EOS procedures, patients will be evaluated for enrollment in HGT-SAN-067 on a case-by-case basis by the investigator. A decision about enrollment will be made following discussion with the medical monitor. If the patient is enrolled, the following assessments are to be repeated within 30 days prior to the first scheduled intrathecal HGT-1410 dose:

- Physical examination
- Height and weight
- Head circumference
- ECG
- Vital signs
- Hematology
- Leukocyte pellet preparation to be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material (if this is not collected at baseline, it can be collected at any subsequent pre-dosing time point)
- Serum chemistry
- Pregnancy testing (for post menarche premenopausal females only)
- Urinalysis
- Urine GAG, including heparan sulfate and heparan sulfate derivatives
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (serum and CSF)
- General anesthesia: administration of anesthesia will be given prior to the following assessments:
- ABR
- MRI of the head
- Neurological examination (performed prior to the administration of anesthesia)

- Full Neurodevelopmental assessments, including Vineland Adaptive Behavior Scales, Second Edition (VABS-II; all assessments performed prior to the administration of anesthesia)
- CSF sample collection (chemistry, cell count, heparan sulfate and heparan sulfate derivatives, and other MPS exploratory biomarkers) via the IDDD
- Children's Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- ITQOL
- Concomitant medications, therapies, and procedures
- AE assessments

8.2 Treatment: Drug Administration and Weekly Assessments – Main or Local Site

Patients will receive HGT-1410 IDDD monthly (Q4W), on Day 2 (±2 days), Week 1.

Patient assessments for safety, biochemical, and neurological baseline measures (Day 1, Week 1) will occur on the day before the first IT injection. Note: Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

CSF samples will be obtained from these patients on Day 2, immediately prior to the first IT study drug injection.

8.2.1 Week 1

8.2.1.1 Day 1 (Pre-treatment) Assessments Performed Prior to Each Dose

- Physical examination
- Height and weight
- Vital signs (may be performed on Day 2 if feasible for the patient to arrive at the study site early in the day and if deemed clinically appropriate by the investigator)
- Hematology (after Month 54 frequency reduced to Q3 Months)
- Serum chemistry (after Month 54 frequency reduced to Q3 Months)
- Urinalysis (after Month 54 frequency reduced to Q3 Months)
- Pregnancy testing (applicable females only)
- Neurological examination (to be performed if symptom directed prior to the administration of anesthesia and the HGT-1410 IT injection and at a minimum of every 12 months)
- Concomitant medications, therapies, and procedures
- AE assessments

Note: If the HGT-SAN-055 EOS (or HGT-SAN-067 Screening) assessments were performed within 7 days of first intrathecal HGT-1410 treatment in this study, the pre-treatment assessments described in this section do not need to be completed prior to the first treatment in study HGT-SAN-067.

DAY 1 (PRE-TREATMENT) ADDITIONAL ASSESSMENTS PERFORMED AT MONTHS 12, 24, 36, 54, 60, 72, 84, 96, AND 102

- Head circumference
- Visual and hearing assessments
- Urine GAG, including heparan sulfate and heparan sulfate derivatives (performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54)
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54)
- ABR (not performed after Month 54, ie not on Months 60, 66, 72, 84, 96, or 102)
- MRI of the head
- Full neurodevelopmental testing, including VABS-II (performed prior to the administration of anesthesia and the HGT-1410 IT injection)
- Children's Sleep Habits Rating Scale
- Child health questionnaire-50
- Child health questionnaire-87
- Infant toddler QoL Questionnaire

8.2.1.2 Day 2 (±2 days) Assessments and Administration of HGT-1410

Patients may be discharged from the clinical site 4 hours after dosing, if deemed stable by the investigator.

- Physical examination (after Month 54 the full physical examination will be performed on an annual basis at Months 66, 78, 90, and 102. The remainder of the physical examinations will be symptom-directed.)
- ECG (performed following IT study drug injection)(after Month 54 performed Q3 months)
- Vital signs (to be performed at the discretion of the investigator)
- CSF sample collection (obtained prior to IT study drug injection)
- HGT-1410 IT injection (Day 2 ±2 days)
- Neurological examination (to be performed if symptom directed and at a minimum of every 12 months)
- Concomitant medications, therapies, and procedures
- AE assessments

The neurological exam should not occur sooner than 4 hours after study drug administration or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

8.3 End of Study/Early Termination Procedures for Treatment Period: Month 103 – Main Site

Patients who complete the study or who discontinue prior to the end of the study during the treatment period, will have EOS assessments performed 30 (±7 days) after their last dose of HGT-1410.

Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation for the treatment period of the study. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Patients should have the IDDD removed when they discontinue from the treatment period of the study, unless the Investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.

Physical examination

- Height and weight
- Head circumference
- Visual and hearing assessment
- ECG
- Vital signs
- Hematology
- Serum chemistries
- Urinalysis
- Pregnancy testing (applicable females only)
- Urine GAG, including heparan sulfate and heparan sulfate derivatives
- Plasma collection for biomarkers
- Anti-rhHNS antibody testing (serum and CSF)
- MRI of the head (unless performed at Month 102)
- CSF sample collection (unless performed at Month 102)
- Neurological examination
- Full neurodevelopmental testing, including VABS-II
- Children’s Sleep Habits Rating Scale
- CHQ-50
- CHQ-87
- Infant toddler QoL Questionnaire
- Concomitant medications, therapies, and procedures
- AE assessments

All patients who discontinue the study early should have their IDDD removed, unless, as indicated above, the Investigator determines that it should not be removed based upon safety assessments.

During the treatment period, patients who withdraw or discontinue after having received fewer than 3 IT injections will not need to complete the EOS visit.

Patients who withdraw or discontinue from the study after having received 3 or more IT injections, will be asked to complete the EOS visit and undergo all the scheduled assessments.

8.4 Safety Follow-up (by Telephone or Visit) Month 104

Patients who complete the study or withdraw early will have a safety follow-up telephone call or visit 30 Days (±7 days) after the last study visit. This will assess:

- Concomitant medications, therapies, and procedures
- AE assessments

8.5 Safety Follow-up Period if Device Not Removed

All patients who do not have the IDDD removed (partial or full device) will have safety follow-up visits every 6 months at the site, with the following assessments performed:

- Informed consent (at the first assessment)
- Symptom-directed PE
- Clinical laboratory tests; only if indicated for a device-related AE
- X-ray monitoring; only for migration or device-related issue
- Concomitant medications, therapies, and procedures; only if indicated for a device-related AE
- AE monitoring only for device-related events

During the 3-year safety follow-up period, the patient may have the device removed at any time, as deemed medically necessary. A post-operative evaluation, including a postoperative check of the incision and collection of safety information, should occur within 1-3 days after the IDDD explantation. An end of study safety follow-up via a phone call should be completed within 14 days after the device removal to collect safety information.

9 QUALITY CONTROL AND ASSURANCE

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

Clinical sites will be monitored by Shire or its designee to ensure the accuracy of data against source documents. The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role in the study, through a password protected environment.

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

SAE information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 General Statistical Methodology

This is an open-label extension of study HGT-SAN-055 to evaluate the long-term safety and clinical outcomes of intrathecal administration of HGT-1410 in patients with MPS IIIA. The statistical methodology supporting the trial will focus on descriptive rather than inferential approaches, given the early phase and objectives of this trial.

Data will be summarized by dose group (10 mg, 45 mg, and 90 mg) with respect to demographic and baseline characteristics, efficacy variables, and safety variables. Summary statistics for continuous variables will include the n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized in a contingency table by the frequency and percentage of patients in each category. Data will be plotted to assess trends across time as appropriate.

No a priori hypotheses will be tested. Exploratory hypotheses may emerge from the data analysis, in which case, appropriate testing methods will be applied and specified in the statistical analysis plan.

There are no formal hypotheses associated with the evaluation of the safety and performance of the IDDD device (SOPH-A-PORT Mini S). All analyses of device safety and performance will be descriptive and no statistical testing will be performed. Device related analyses will be based on patients for whom the device implant procedure was performed and are described in the sections below.

10.2 Determination of Sample Size

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

10.3 Analysis Populations

The primary analysis population consists of all eligible patients from HGT-SAN-055 who have agreed to participate in the extension study. This population will be used to perform both safety and efficacy analyses. The collection of detailed data pertaining to the SOPH-A-PORT mini S will permit device-related analyses to be conducted in the subset of patients in the primary analysis population who had the SOPH-A-PORT Mini S implant procedure performed.

10.4 Demographics and Baseline Characteristics

Patient disposition for those enrolled will be presented in a summary table using number and percentage of patients enrolled, completed or discontinued/withdrew. The reasons for discontinuation/withdrawal will also be presented.

Demographic and baseline characteristics (eg, age, race, ethnicity, medical history, and surgical history) will be reported in summary tables.

10.5 Statistical Analysis of Pharmacokinetic Variables

Not applicable.

10.6 Efficacy, Safety, and Pharmacodynamic Evaluations

10.6.1 Primary Analyses

10.6.1.1 Safety Analysis

In general, safety assessments will be based on all assessments post-baseline. The assessment of safety will be based primarily on the frequency of AEs, and on the frequency of clinically notable abnormal vital sign and laboratory values. Changes from baseline will be calculated by subtracting the baseline value from the post-baseline value.

All enrolled patients who had an IDDD surgical procedure and/or received administration of HGT-1410 will be included in the safety analysis.

Adverse events will be recorded throughout the study and at early termination. Adverse events and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be summarized by presenting, for each dose group during the treatment period, the number and percentage of patients having any AE, having an AE in system organ class, and having each individual AE. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events , defined as all AEs from the time of the surgery for IDDD implantation to the last follow up contact, ie, 30 days after the last HGT-1410 administration, (new or worsened from baseline) during the treatment period, will be summarized by system organ class, severity, type of adverse event and relationship to trial medication/procedure.

Treatment-emergent AEs, of the treatment period, deemed related to HGT-1410 administration will be summarized separately.

IDDD and procedure-related AEs will be summarized within system organ class by preferred term. IDDD and procedure-related AEs will be tabulated by severity (mild, moderate, severe) and degree of relatedness. Separate tabulations will be provided for adverse events related to the IDDD, device surgical procedure (including post-implant infections) and IT administration process. These summaries will be presented by device and overall, as appropriate.

Descriptive summaries of clinical laboratory evaluations (hematology, serum chemistry, urinalysis and CSF) results will be presented in summary tables by evaluation visit. Changes from baseline will be summarized for each post-baseline visit. Each laboratory result will be categorized as a patient having had (1) an Abnormal and Clinically Significant (CS) value at any time, (2) no CS values at any time but had at least one Abnormal and not CS (NCS) value, and

(3) no CS or NCS values at any time; the number and percentage in each category will be presented. For any patient who experiences a CS laboratory result at any time 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.

The observed values and changes from baseline for vital sign data will be summarized for each dose group. Shift tables may be presented, utilizing reference ranges. Patients with notably abnormal values will be identified and listed separately along with their values.

The observed values and changes from baseline for ECG data will be summarized for each dose group. Patients with any clinically significant findings and/or conduction abnormalities will be listed separately along with their values.

Anti-rhHNS antibody formation will be monitored throughout the study. Results will be presented in summary tables by number and percentage of positive and negative specimens by evaluation visit, and number and percentage of positive and negative specimens overall. The effect of antibodies on other safety parameters will be assessed by presenting summary tables by antibody status.

For those patients who fail to complete the study, the reason for discontinuation will be listed by patient and dose group.

Listings of all study safety data will be presented.

10.6.2 Other Observations Related to Safety

10.6.2.1 IDDD Performance

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

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

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

10.6.3 Secondary Analysis

10.6.3.1 Clinical Assessments

The change from baseline in neurocognitive assessment based scores will be examined by dose group. Furthermore, the effect of HGT-1410 administration on QoL measures will be examined by presenting mean change from baseline by dose groups. Other relevant assessments which might help in the understanding of clinical activity will also be analyzed.

10.6.3.2 Pharmacodynamic Analyses

To determine the effects of HGT-1410 administration on biomarkers, mean change from baseline will be assessed at selected time points. The heparan sulfate reduction (in CSF) will be examined using mean change and the corresponding 95% confidence interval. Other exploratory biomarkers in CSF, serum, and urine may also be examined.

The effect of anti- rhHNS antibodies on the changes in CSF biomarkers may also be examined by presenting summary tables by antibody status.

10.6.4 Interim Analysis

Interim analyses may be conducted before trial completion for safety monitoring, regulatory reporting, publication or general study planning purposes. Analyses will be descriptive in nature, with no formal comparisons planned and no hypotheses formally tested.

The planned final analyses and presentations will be defined in the Statistical Analysis Plan (SAP).

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

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

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

11.2 Institutional Review Board or Independent Ethics Committee Approval

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

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

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonization (ICH) GCP Guidelines.

11.4 Patient Information and Consent

Before enrolling in the clinical study, the patient's parent(s), or the patient's legally authorized representative(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent form that includes information about the study will be prepared and given to the patient's parent(s), or the patient's legally authorized representative(s). This document will contain all FDA and ICH-required elements.

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

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

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

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

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

Where applicable, signed assent(s) to participate in the study must be obtained.

11.5 Patient Confidentiality

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

11.6 Study Monitoring

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

The study will be monitored by the sponsor or its designee. On site monitoring will be performed by a representative of the sponsor (clinical study monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, telephone, and facsimile).

11.7 Case Report Forms and Study Records

Case report forms are provided for each patient in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the CRFs.

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

11.7.1 Critical Documents

Before Shire initiates the trial (ie, obtains informed consent [assent if applicable] from the first patient), it is the responsibility of the investigator to ensure that the following documents are available to Shire or their designee:

- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed or supported by an official regulatory document)
- Current medical license of investigator and sub-investigator(s)
- Signed and dated agreement of the final protocol
- Signed and dated agreement of any amendment(s), if applicable
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed: protocol, any amendments, Patient Information/Informed Consent Form (Assent form if applicable), and any other written information to be provided regarding patients recruitment procedures
- Copy of IRB/IEC approved Patient Information/Informed Consent Form (Assent Form if applicable)/any other written information/advertisement
- Any additional regulatory approvals, ie national regulatory approvals
- List of IRB/IEC Committee members/constitution
- Financial agreement(s)
- Documentation from central or local laboratory as applicable
    - Reference ranges
    - Certification/QA scheme/other documentation

Regulatory approval and notification as required must also be available; these are the responsibility of Shire. All trial documents will be available in a Trial Master File (TMF) at the investigator/trial site and at Shire.

11.8 Device Failure Review Process

The final cause for device failures will be reviewed by a Shire team by examining the clinical database, safety database, and manufacturer investigation of returned devices.

11.9 Protocol Violations/Deviations

The investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations. A record of patients screened, but not entered into the study, is also to be maintained. There will be no protocol exemptions granted for this study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact the sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also be required to be submitted to the IRB/IEC.

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

11.10 Access to Source Documentation

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

11.11 Data Generation and Analysis

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

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

11.12 Premature Closure of the Study

11.12.1 Study Termination

If the sponsor or an investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable patient risk, the study may be terminated after appropriate consultation between Shire and the investigators. In addition, a decision on the part of Shire to suspend or discontinue development of the study material may be made at any time.

11.12.2 Site Termination

A specific site may be terminated separate from the general study for, but not limited to, the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at the site.
- Failure of the investigator to enter patients at an acceptable rate.
- Insufficient adherence by the investigator to protocol requirements.

11.13 Retention of Data

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

Biological samples may be reserved for potential, future, biomarker studies (see Section 7.7.7).

11.14 Financial Disclosure

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

11.15 Publication and Disclosure Policy

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

It is understood by the investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies.

In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study in a timely manner.

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

Shire may perform analyses of interim and/or final locked study data for the purpose of publication.

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Appendix 1 Schedule of Events

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)						
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	
Informed Consent/Enrollment		●						
Physical Examination	●	●[p]	●[p]	●[p]				
Symptom-Directed Physical Examination		●[p]	●[p]				●	
Neurological Examination[h]	●	●[s]	●[s]				●	
Height and Weight	●	●					●	
Head Circumference	●			●			●	
Visual and Hearing Assessment				●			●	
ECG	●		●[b]				●	
Vital Signs	●	●[s]	●[s]				●	
Hematology	●	●					●	
Serum Chemistry	●	●					●	
anti-rhHNS antibody testing (serum)[k]	●			●[t]	●[t]		●	
Plasma storage for biomarkers	●	●		●			●	
Pregnancy Testing[l]	●	●					●	

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)						
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	
Urinalysis	●	●					●	
Urine GAGs	●			●[t]	●[t]		●	
Leukocyte pellet preparation[m]	●							
CSF chemistry and cell counts[c]	●	●					●	
CSF sample storage[c,o]	●	●					●	
CSF Heparan Sulfate and Heparan Sulfate Derivatives[c]	●			●[t]	●[t]	●		
Anti-rhHNS antibody testing (CSF)[c]	●			●[t]	●[t]		●	
Auditory Brainstem Response (ABR)[q]	●			●				
MRI of the Head	●			●			●[n]	
HGT-1410 dosing: every 28 (±7) days[d,g]			●					
Full Neurodevelopmental Testing[i]	●			●			●	
Children's Sleep Habits Rating Scale	●			●			●	
Child Health Questionnaire-50	●			●			●	
Child Health Questionnaire-87	●			●			●	
Infant Toddler QOL Questionnaire	●			●			●	

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment		Month 7 through Month 104 (from the start of HGT-SAN-055)						
		Dosed every 28 (±7) days (ie, Q4W)						
	Screening/or HGT-SAN-055 EOS Visit[i] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	
Concomitant Medications, Therapies, and Procedures	●	●	●				●	●
Adverse Event Monitoring	●	●	●				●	●

Abbreviations: ABR = Auditory brainstem response; CSF = cerebrospinal fluid; EOS = end of study ; ECG = electrocardiogram; IT = intrathecal; MRI = Magnetic resonance imaging; TX = treatment

Note: The timing of assessments is calculated from the start of HGT-SAN-055. Therefore, for example, the end-of-study visit, as presented here at Month 102, corresponds to Month 102 in HGT-SAN-067, but represents a total of 102 months of study treatment (102 months in HGT-SAN-067 + 6 months in HGT-SAN-055).

[a] Week 1 only, and only performed if >7 days have elapsed since HGT-SAN-055 EOS visit assessments.

[b] ECG to be performed following administration of study drug, after Month 54 it is to be performed every 3 months.

[c] CSF samples will be obtained according to the process within the study laboratory manual. An attempt will be made to obtain a CSF sample via the IDDD prior to each administration of HGT-1410 and at the End of Study visit. If it is not possible to obtain a CSF using the IDDD, the IDDD may be replaced (up to twice in a 6 month period [including the time in the HGT-SAN-055 study]) or an LP may be performed.

[d] Patients may be discharged as early as 4 hours post HGT-1410 infusion (ie, on Day 2) when deemed clinically stable by the investigator.

[e] All patients who complete the study will have end of study assessments performed 30 (±7 days) after their last dose of study drug.

[f] A safety follow up telephone call will be made 30 (±7 days) after End of Study Procedures.

[g] If a patient's IDDD becomes nonfunctional or infected; it will be replaced (up to 2 times in a 6 month period; including the time in Study HGT-SAN-055).

[h] The neurological exam should not occur sooner than 4 hours after administration of study drug or before the patient has fully recovered from any anesthesia administered for the dosing, whichever occurs later.

[i] Full neurodevelopmental testing includes an assessment with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II).

Table A1-1 HGT-SAN-067 Study Assessments for Patients Who Have Received 6 Months of HGT-1410 Treatment in Study HGT-SAN-055

Assessment			Month 7 through Month 104 (from the start of HGT-SAN-055)					
		Dosed every 28 (±7) days (ie, Q4W)						
	Screening/or HGT-SAN-055 EOS Visit[j] (Month 6 from the start of HGT-SAN-055)	Pre-Tx Day 1[a]	IT dosing Day 2 (±2)	Months 12, 24, 36, 54, 60, 72, 84, 96 and 102 (from the start of HGT-SAN-055)	Additional Assessments at Months 66, 78, and 90 (from the start of HGT-SAN-055)	Months 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 48, and 51 (from the start of HGT-SAN-055)	EOS[e] Month 103 (from the start of HGT-SAN-055)	Month 104 Safety Follow-up[f]
	Main Site only	Main or Local Site	Main or Local Site	Main Site only	Main Site only	Main Site only	Main Site only	

[j] Assessments will be required only if more than 60 days have elapsed following the HGT-SAN-055 procedures. These assessments would be repeated within 30 days prior to the first scheduled HGT-1410 IT dose.

[k] Blood sample drawn before IT injection of HGT-1410.

[l] A pregnancy test will be carried out on pre-treatment Day 1 in females who are postmenarche to premenopause (childbearing). The results must be negative before study drug can be administered.

[m] A blood sample for leukocyte pellet preparation is to be taken at baseline, before dosing. This pellet should be stored frozen, and will be used for additional disease-related laboratory studies, including possible assessment of cross-reactive immunologic material. If this is not drawn at baseline, it can be drawn at any subsequent visit, but it must be taken before dosing. This only needs to be taken once during the study.

[n] These assessments are not to be performed at an EOS visit conducted at Month 103 if they were performed at the Month 102 visit.

[o] CSF samples will be tested for MPS exploratory biomarkers, and possibly extractables and leachables.

[p] After Month 54 the Symptom-Directed PE is to be done monthly. Full PE is done monthly to Month 54 and then at least yearly (ie, Months 66, 78, 90, and 102), or more frequently at the investigator's discretion. Genitourinary AEs may be evaluated by the patient's primary care physician and a follow-up report will be sent to the study site.

[q] ABR will not be performed after Month 54.

[r] Informed consent will be obtained at Screening and Month 54.

[s] These Day 1 assessments may be performed on the same day as the administration of study drug (Day 2). This can occur if it is feasible for the patient to arrive at the study site early in the day, and if it is deemed clinically appropriate by the investigator. If the procedures on Day 1 and Day 2 are combined in this way, the assessments will be recorded as occurring on Day 2.

[t] Urine GAG, including heparan sulfate and heparan sulfate derivatives, and anti-rhHNS antibody testing will be performed at Months 60, 66, 72, 78, 84, 90, and 96, ie, Q6 Months following Month 54); these assessments must be performed at the main site.

Table A1-2 HGT-SAN-067 Study Assessments for the Safety Follow-up Period for Patients with Implanted Partial or Full Device After Treatment Completion

Procedure	Every 6 Months from Last Visit (±14 Days)[b]	End of Study		
		Device Explantation[e] Day 1	Post-operative Evaluation Days 2-4[f]	Safety Follow-up Call 14 days post device explantation
Informed consent[a]	●			
Symptom-directed PE	●		●	
Hematology[c]	●			
Serum chemistry[c]	●			
Urinalysis[c]	●			
Standard CSF safety labs[c]	●			
X-ray[d]	●			
Con meds, therapies, and procedures	●	●	●	●
Device-related AE monitoring	●	●	●	●
Postoperative check of IDDD incision			●	

Abbreviations: AE= adverse event; IDDD= intrathecal drug delivery device; PE=physical examination

[a] Informed consent will be captured at the first 6 month visit after the end of the treatment period.

[b] From the patient's last follow-up visit and every 6 months thereafter up until the device is removed

[c] To be acquired only as indicated by a device-related AE.

[d] To check IDDD placement or for any device-related AEs.

[e] During the 3-year safety follow-up period, the patient may have the device removed at any time, as deemed medically necessary

[f] Post-operative evaluation can occur within 1-3 days after IDDD explantation.

Appendix 2 Neurodevelopmental and Behavioural Assessments

Tables A2-1 and A2-2 detail the specific psychometric instruments that will be used to provide measures of each of relevant neurobehavioral or developmental domain assessed. The tables also summarize the rules used to select a test for a patient, the subtests included in each test, and the subscales generated by the test battery.

Table A2-1 Summary of Neurodevelopmental Outcome Measures

Domain	Age	Test
Summary score and subdomains: - Cognitive - Motor - Social/Emotional	0 to 42 months	Bayley Scales of Infant Development, Third Edition (BSID-III)[23]
- Cognitive - Processing skills	3 to 18 years	Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]
Motor	3.0 to 16:11 years	Movement Assessment Battery for Children, Second Edition (MABC-2)[25]
Communication Daily Living Socialization Motor Skills	0 to 90 years	Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Table A2-2 Summary of Sanfilippo-specific Assessments

Domain	Assessment
Parent-scored behavioral inventory - communication: understanding - communication: expression - tantrums - specific behaviors inventory - mood & emotions inventory	Sanfilippo Behavior Rating Scale
MPS-specific four-point scoring system/total disability score - cognition - expressive language - motor score	Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The term “neurodevelopmental” refers to the process by which the neurological system matures and changes over time. Assessing these changes in a population of children whose neurological system is progressively more affected can be very challenging.

Typically, neurodevelopmental progress is reflected by the child's abilities to perform certain skills (sitting, walking, and talking).

However, a child with a neurological disorder may be able to perform age appropriate skills, but with atypical patterns. For example, the child may be able to walk, but his gait is not normal. Most assessments will therefore measure the skills, but are not designed to capture the abnormalities in pattern or quality of the skill.

These qualitative differences will be evident to the skilled test administrator/clinician who is familiar with the disorder. However, only longitudinal tracking and repeated measures will reveal the significance of these abnormalities in overall function to the less experienced clinician.

The rate at which different skills develop or regress over time will give insight into the disease process. The next step is to determine how the learned skills are used for daily functional activities so that as the children grow up they become independent from caregivers. These functional skills can be tracked to reflect quality of life issues for both parents and children.

Neurodevelopmental assessments described below will be scheduled for administration in the morning and estimated to last between 2 and 4 hours.

The list of assessments and algorithm is discussed in detail in the Study Operations Manual and includes:

Bayley Scales of Infant Development, Third Edition (BSID-III)[23]

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 to 42 months. This measure consists of a series of developmental play tasks and takes between 45 and 60 minutes to administer. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Kaufman Assessment Battery for Children, Second Edition (KABC-II)[24]

Purpose:

The KABC-II measures a child's cognitive ability and processing skills and was designed to minimize verbal instructions and responses. In addition, the assessment contains little cultural content to provide a more accurate assessment of children from diverse backgrounds. Thus language difficulties or cultural differences are minimized in the test battery's results.

Description:

Investigators may choose either the Cattell-Horn-Carroll or the Luria model for a patient's assessment.

The Cattell-Horn-Carroll model is used with children from a mainstream cultural and language background and the Luria model is used for children with significantly limited verbal ability. Subtests are administered on four or five ability scales and interpreted using the chosen model.

Movement Assessment Battery for Children, Second Edition (MABC-2)[25]

Purpose:

The Movement Assessment Battery for Children, Second Edition identifies, describes and guides treatment of motor impairment in children from 3.0 to 16:11 years of age.

Description:

The MABC-2 checklist is administered individually over approximately 30 minutes. It yields both normative and qualitative measures of movement competence, manual dexterity, ball skills, static and dynamic balance.

Vineland Adaptive Behavior Scales, Second Edition (VABS-II)[26]

Purpose:

The 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. It encompasses ages from birth to 90 years.

Description:

Adaptive behavior is a composite of various dimensions. This test measures 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional) and is administered in a semi-structured interview in through a questionnaire. The scales of the VABS-II were organized within a 3-domain structure: Communication, Daily Living, and Socialization. This structure corresponds to the 3 broad domains of adaptive functioning by the American Association of Intellectual and Developmental Disabilities: Conceptual, Practical, and Social. In addition, VABS-II offers a Motor Skills Domain and an optional Maladaptive Behavior Index. The scores are interpreted by means of score equivalents for the raw scores in each domain, percentile ranks, age equivalents, adaptive levels, and maladaptive levels.

Sanfilippo Behavior Rating Scale (SBRS)

The Sanfilippo Behavior Rating Scale (SBRS) is a newly-developed scale designed by Drs. Elsa Shapiro and Michael Potegal to measure a cluster of behaviors known to occur in Sanfilippo syndrome. The SBRS is a parent-scored behavioral inventory measuring (1) comprehensive language skills, (2) expressive language skills, (3) tantrums, (4) mood and emotions, and (5) other behaviors not otherwise classified.

Four-Point Scoring System/Total Disability Score (FPSS/TDS)[5]

The FPSS assesses motor function, expressive language, and cognitive function on a 0 to 3 point scale and can be used for individuals of all ages. The total disability score is the average of the motor function, speech, and cognitive function scores.

Appendix 3 Expected Adverse Device Effects

Procedure-Related Complications

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

Intrathecal Access Complications

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

System-Related Complications

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

Appendix 4 Protocol Amendment 8 Summary of Changes

AMENDMENT SUMMARY AND RATIONALE

Clinical protocol HGT-SAN-067 has been amended to include language to allow for patients to retain a full or partial IDDD in situ after they discontinue or complete the treatment period of the study, at the discretion of the investigator based upon safety assessment. These patients who do not have the IDDD removed at the end of the treatment period will continue to be observed during a safety follow-up period with visits every 6 months to evaluate patient safety of the device up to an additional 3 years or until the device is removed in the last patient.

Previous Amendment: Amendment 7, 08 February 2016

DETAILED SUMMARY OF CHANGES FOR THE AMENDMENT

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below. **Bold** text indicates new text. ~~Strikethrough~~ text indicates deleted text.

Change: Clarification that explantation events will be included as SOPH-A-PORT Mini S assessments.
Section impacted by this change: Section 3.3, SOPH-A-PORT Mini S Assessments
Revised Text: For the subset of patients who will have a PORT-A-CATH IDDD replaced by a SOPH-A-PORT Mini S, information relative to the safety and performance of the SOPH-A-PORT Mini S will be collected in a structured manner. SOPH-A-PORT Mini S assessments will include measures of device implantation, device function, device longevity, record of revisions, ~~removals~~**explantation events**, and replacements of the implanted IDDD, and AEs associated with the device. These data will be collected in the patient's electronic case report form (eCRF) from the time of implantation and continue through the study as long as the SOPH-A-PORT Mini S remains implanted.
Other sections impacted by this change: Synopsis; Section 7.11, Device Data

Change: Clarification that if a patient is discontinued from the study, the IDDD should be removed and a modified end of study visit completed. However, if the IDDD is not removed, the patient will continue to be observed during a safety follow-up period with visits every 6 months until the IDDD has been fully explanted.
Section impacted by this change: Section 4.1, Overall Study Design and Plan
Revised Text: All patients will have received a series of standardized neurodevelopment assessments; in the HGT-SAN-055 study, these will have occurred at Baseline and either prior to or at the 6-month time point. Patients will continue in HGT-SAN-067, **during the treatment period,** with whichever age specific assessment they began with in HGT-SAN-055. If, however, a patient's capability improves and they become capable of completing

assessments at a higher level, such additional assessments may be added. Any additional assessments are to be performed after the original assessments (those used in study HGT-SAN-055) have been carried out**, during the treatment period of the study**.

An MRI of the head will be performed at Months 12, 24, 36, 54, 60, 72, 84, 96, and 102 and ABR testing will be performed at Months 12, 24, 36 and 54 (note that assessment time point nomenclature includes the 6 months in the HGT-SAN-055 study)**, during the treatment period of the study**.

In the event of a device malfunction, X-rays may be performed to investigate, as well as to verify correct catheter and port placement following surgical IDDD implantation or revision. In addition, fluoroscopy may be employed intra-operatively to guide catheter placement. Patients may undergo 3 X-ray examinations in association with each episode of IDDD malfunction and subsequent IDDD revision or replacement. The number of IDDD revisions/replacements is limited to 2 in any 6-month period (including the time in the HGT-SAN-055 study), and the number of protocol-associated X-ray evaluations is limited to 6 exposures in any 6-month period (including time in study HGT-SAN-055). ~~If patients are to continue to receive HGT-1410 using the IDDD beyond the duration of this study, they will also have X-ray examinations of the device performed at the EOS visit, to document correct positioning.~~

…

All patients will have an EOS visit **during the treatment period,** 30 (±7) days following their last administration of HGT-1410 (ie, Month 102). The EOS procedures will include standard clinical laboratory tests (serum chemistry, hematology, and urinalysis) in CSF and blood, protocol specific laboratory testing (eg, anti-rhHNS antibody testing), neurodevelopmental testing, child health questionnaires, and MRI. Use of concomitant medications, therapies, and procedures will be recorded and AEs will be monitored.

All patients will be contacted by telephone or will have a visit for a Final Safety Follow-up, conducted at 30 (±7) days after the EOS visit**, of the treatment period,** (ie, Month 103) to collect updated information on AEs and concomitant medications, therapies, and procedures.

If the patient is discontinued from the study, the IDDD should be removed and a modified end of study visit should be completed within 30 days after withdrawal. These visits may be combined into one visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. If the investigator determines that the IDDD should not be removed from the patient based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit.

…

If there is no significant safety risk in the opinion of the investigator, a non-functional

IDDD may be left in situ for up to 3 months **during the treatment period**.

Patients who discontinue or are withdrawn before receiving 3 monthly IT injections will not have to undergo the EOS evaluations but will have their IDDD removed.

If **during the treatment period,** a patient discontinues, or withdraws from the study, or the study is stopped by the sponsor, the IDDD **should** ~~will~~ be removed ~~as part of the EOS Procedures.~~ **unless the Investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.**

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.

An overview of the study appears in the Schedule of Events (Appendix 1). **See Appendix 1, Table A1-2 for the Study Schedule of Events for the safety follow-up period for patients with partial or full devices in place after the end of the treatment period.**

Other sections impacted by this change: Synopsis; Section 7.13.4, Device Removal

Change: Definition provided for LPLV and clarification that the study duration has been extended to up to an additional 3 years or until the device is removed in the patient, for patients with a partial for full device in place after the treatment period.

Section impacted by this change: Section 4.3, Study Duration and Dates

Revised Text:

Patients with a partial or full device still in place after completion of the treatment period, may be followed for safety up to an additional 3 years or until the device is removed in the last patient.

The LPLV will be the safety follow-up visit after the final device (partial and/or full) is removed from the last patient during the safety follow-up period.

Other sections impacted by this change: Synopsis

Change: Informed consent will be obtained from patients who did not have the device removed.

Section impacted by this change: Section 7.1, Informed Consent

Revised Text:

After the treatment period ends, informed consent from patients who do not have the

IDDD removed (partial or full device) will be obtained for the safety follow-up period.
Other sections impacted by this change: NA

Change: Symptom-directed physical examinations to be performed during the safety follow-up period.
Section impacted by this change: Section 7.2, Physical Examination
Revised Text: A full physical examination or a symptom-directed physical examination of each patient will be performed at time points detailed in Appendix 1 **Table A1-1** Schedule of Events, **for the duration of the treatment period. The physical examinations for the safety follow-up period will be symptom-directed, see Appendix 1, Table A1-2 Schedule of Events for details.**
Other sections impacted by this change: NA

Change: Clinical laboratory testing only performed for device-related AEs during the safety follow-up period.
Section impacted by this change: Section 7.7, Clinical Laboratory Tests
Revised Text: **For patients who do not have the IDDD removed (partial or full device) at the end of the treatment period, clinical laboratory testing will only be performed when indicated for a device-related AE during the safety follow-up period.**
Other sections impacted by this change: NA

Change: Clarification regarding x-ray verification during safety follow-up period.
Section impacted by this change: Section 7.13.2, X-ray Verification of Intrathecal Drug Delivery Device Placement
Revised Text: A postoperative x-ray check of the IDDD will be performed following surgery to verify proper installation and confirmation of IDDD placement at the mid-thoracic level. The x-rays may be performed to check placement of the device, **migration, or malfunction of the device** as needed, throughout the **treatment period or the safety follow-up period of the** study. ~~If the patient is to receive intrathecal HGT-1410 beyond the end of the study, an X-ray will be performed at the end of the study to verify that the IDDD is in the correct position~~. At a minimum, the date of the x-ray verifying correct IDDD placement will be documented on the patient's eCRF. If the device requires revision or replacement during **the treatment period of** the study, additional x-rays will be taken to document proper positioning of the device. If an IDDD malfunctions, an x-ray may be performed to assess the potential cause of malfunction. Fluoroscopy may be used during device implant or

revision procedures.
Other sections impacted by this change: NA

Change: Final evaluation in the safety follow-up period defined.
Section impacted by this change: Section 7.26, Removal of Patients from the Trial or Study Drug
Revised Text: At the time of discontinuation or withdrawal, patients will be asked to participate in all safety and efficacy evaluations required for the end of study visit and for the safety follow-up visit **for the treatment period of the study**. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. The patient ~~will~~ **should** be scheduled for the removal of the IDDD. **The final evaluation in the safety follow-up period for patients who do not have the IDDD removed (full or partial device) is defined as the follow-up evaluation performed for up to 3 years after the treatment period ends.**
Other sections impacted by this change: NA

Change: Study discontinuation process defined.
Section impacted by this change: Section 7.27, Study Discontinuation Process
Revised Text: **If the patient is discontinued from the study, the IDDD should be removed and a modified end of study visit should be completed within 30 days after withdrawal. These visits may be combined into one visit, in which case follow-up via a phone call should be completed within 14 days after the device removal to collect safety information. The end of study visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution.** **If the investigator determines that the IDDD should not be removed from the patient based upon a safety assessment and the IDDD (full or partial) remains in the patient, then the patient will continue in the study under the safety follow-up period upon completion of their last treatment period visit. This last treatment period visit only requires collection of safety assessments, including symptom-directed physical exam, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), concomitant medications, therapies, and procedures, and AE monitoring. No MRI or cognitive assessments are required. No study-required CSF collection is needed at the IDDD removal, unless required for AE resolution. Once the patient completes their last treatment period visit, they will return for their first safety follow up visit**

in six months. The patient will continue in the safety follow-up period with a clinic visit every 6 months for up to 3 years or until the device is removed in the last patient. An end of study follow-up via a phone call should be completed within 14 days after the device removal to collect safety information (refer to Section 8.5).
Other sections impacted by this change: NA

Change: Clarification regarding the EOS/early termination procedures for the treatment period.
Section impacted by this change: Section 8.3, End of Study/Early Termination Procedures **for Treatment Period**: Month 103 – Main Site
Revised Text: Patients who complete the study or who discontinue prior to the end of the study **during the treatment period**, will have EOS assessments performed 30 (±7 days) after their last dose of HGT-1410. Patients who discontinue or are withdrawn prior to study completion will be asked to participate in the EOS procedures at the time of discontinuation **for the treatment period of the study**. Participation in these EOS procedures will be strongly encouraged, but is voluntary for those patients electing to discontinue from the study. Note: Patients ~~will~~ **should** have the IDDD removed when they discontinue from the **treatment period of the** study, unless the ~~patient is continuing to receive treatment through another mechanism (eg, extension study, expanded access, commercially available).~~ **Investigator determines that it should not be removed based upon safety assessments. The device can remain in the patient (partial [catheter only] or full [port, catheter, and suture wings]) if the patient is doing clinically well and there are no further known risk factors such as infection (eg, meningitis). The device may be partially or fully removed as medically required and determined by the neurosurgeon at a future date.** … All patients who discontinue the study early ~~will~~ **should** have their IDDD removed, **unless, as indicated above, the Investigator determines that it should not be removed based upon safety assessments.** Patients who withdraw or discontinue after having received fewer than 3 IT injections **during the treatment period** will not need to complete the EOS visit.
Other sections impacted by this change: NA

Change: Assessments during safety follow-up period if device not removed described.
Section impacted by this change: Section 8.5, Safety Follow-up Period if Device Not Removed
Revised Text:

All patients who do not have the IDDD removed (partial or full device) will have safety follow-up visits every 6 months at the site, with the following assessments performed:

- **Informed consent**
- **Symptom-directed PE**
- **Clinical laboratory tests; only if indicated for a device-related AE**
- **X-ray monitoring; only for migration or device-related issue**
- **Concomitant medications, therapies, and procedures; only if indicated for a device-related AE**
- **AE monitoring only for device-related events**

During the 3-year safety follow-up period, the patient may have the device removed at any time, as deemed medically necessary. A post-operative evaluation, including a postoperative check of the incision and collection of safety information, should occur within 1-3 days after the IDDD explantation. An end of study safety follow-up via a phone call should be completed within 14 days after the device removal to collect safety information.

Other sections impacted by this change: Table A1-2, HGT-SAN-067 Study Assessments for the Safety Follow-up Period for Patients with Implanted Partial or Full Device After Treatment Completion

Change: Clarification regarding statistical analysis of TEAEs and treatment period.

Section impacted by this change: Section 10.6.1.1

Revised Text:
Adverse events will be summarized by presenting, for each dose group **during the treatment period**, the number and percentage of patients having any AE, having an AE in system organ class, and having each individual AE. In addition, those events which resulted in death or were otherwise classified as serious will be presented in a separate listing. The incidence of treatment-emergent adverse events , defined as all AEs from the time of the surgery for IDDD implantation to the last follow up contact, ie, 30 days after the last HGT-1410 administration, (new or worsened from baseline) **during the treatment period,** will be summarized by system organ class, severity, type of adverse event and relationship to trial medication/procedure.

Treatment-emergent AEs**, of the treatment period,** deemed related to HGT-1410 administration will be summarized separately.

Other sections impacted by this change: NA

Change: Language added indicating interim analysis may be performed.

Section impacted by this change: Section 10.6.4, Interim Analysis

Revised Text: **Interim analyses may be conducted before trial completion for safety monitoring, regulatory reporting, publication or general study planning purposes. Analyses will be descriptive in nature, with no formal comparisons planned and no hypotheses formally tested.** ~~No formal analysis or interim statistical testing for early stopping of the trial is planned. Descriptive analyses of the data before trial completion may be performed for safety monitoring, regulatory reporting, publication, or general planning purposes.~~
Other sections impacted by this change: NA

Appendix 5 Protocol Signature Page

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 Amendment 7
Final Date:	21 June 2010
Amendment 1 Date:	22 January 2011
Amendment 2 Date:	13 January 2012
Amendment 3 Date:	28 August 2012
Amendment 4 Date:	3 May 2013
Amendment 5 Date:	17 January 2014
Amendment 6 Date:	10 July 2014
Amendment 7 Date:	08 February 2016
Amendment 8 Date:	01 February 2017

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

Signatory:

Investigator

_____
Signature **Date**

_____
Printed Name

I have read and approve the protocol described above.

Signatory:

Shire Medical Monitor

[redacted] [redacted]

_____
Signature **Date**

[redacted] DO

_____
Printed Name

Appendix 6 The National Cancer Institute Common Terminology Criteria version 3.0

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.
The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.
Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

ALLERGY/IMMUNOLOGY

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Allergic reaction/ hypersensitivity (including drug fever)	Allergic reaction	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).						
ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – *Select* in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death
Allergy/Immunology – Other (Specify, __)	Allergy – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

AUDITORY/EAR

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Earache (otalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]	Hearing (monitoring program)	Threshold shift or loss of 15 – 25 dB relative to baseline, averaged at 2 or more contiguous test frequencies in at least one ear; or subjective change in the absence of a Grade 1 threshold shift	Threshold shift or loss of >25 – 90 dB, averaged at 2 contiguous test frequencies in at least one ear	Adult only: Threshold shift of >25 – 90 dB, averaged at 3 contiguous test frequencies in at least one ear Pediatric: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., ≥20 dB bilateral HL in the speech frequencies; ≥30 dB unilateral HL; and requiring additional speech-language related services)	Adult only: Profound bilateral hearing loss (>90 dB) Pediatric: Audiologic indication for cochlear implant and requiring additional speech-language related services	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1]	Hearing (without monitoring program)	—	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)	—
REMARK: Pediatric recommendations are identical to those for adults, unless specified. For children and adolescents (≤18 years of age) without a baseline test, pre-exposure/pre-treatment hearing should be considered to be <5 dB loss.						
Otitis, external ear (non-infectious)	Otitis, external	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Otitis, middle ear (non-infectious)	Otitis, middle	Serous otitis	Serous otitis, medical intervention indicated	Otitis with discharge; mastoiditis	Necrosis of the canal soft tissue or bone	Death

AUDITORY/EAR						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Tinnitus	Tinnitus	—	Tinnitus not interfering with ADL	Tinnitus interfering with ADL	Disabling	—
ALSO CONSIDER: Hearing: patients with/without baseline audiogram and enrolled in a monitoring program[1]; Hearing: patients without baseline audiogram and not enrolled in a monitoring program[1].						
Auditory/Ear – Other (Specify, __)	Auditory/Ear – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[1] Drug-induced ototoxicity should be distinguished from age-related threshold decrements or unrelated cochlear insult. When considering whether an adverse event has occurred, it is first necessary to classify the patient into one of two groups. (1) The patient is under standard treatment/enrolled in a clinical trial <2.5 years, and has a 15 dB or greater threshold shift averaged across two contiguous frequencies; or (2) The patient is under standard treatment/enrolled in a clinical trial >2.5 years, and the difference between the expected age-related and the observed threshold shifts is 15 dB or greater averaged across two contiguous frequencies. Consult standard references for appropriate age- and gender-specific hearing norms, e.g., Morrell, et al. Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. Journal of the Acoustical Society of America 100:1949-1967, 1996; or Shotland, et al. Recommendations for cancer prevention trials using potentially ototoxic test agents. Journal of Clinical Oncology 19:1658-1663, 2001.

In the absence of a baseline prior to initial treatment, subsequent audiograms should be referenced to an appropriate database of normals. ANSI. (1996)

American National Standard: Determination of occupational noise exposure and estimation of noise-induced hearing impairment, ANSI S 3.44-1996. (Standard S 3.44). New York: American National Standards Institute. The recommended ANSI S3.44 database is Annex B.

BLOOD/BONE MARROW

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or ≤25% reduction from normal cellularity for age	Moderately hypocellular or >25 – ≤50% reduction from normal cellularity for age	Severely hypocellular or >50 – ≤75% reduction cellularity from normal for age	—	Death
CD4 count	CD4 count	<LLN – 500/mm^3 <LLN – 0.5 x 10^9 /L	<500 – 200/mm^3 <0.5 – 0.2 x 10^9 /L	<200 – 50/mm^3 <0.2 x 0.05 – 10^9 /L	<50/mm^3 <0.05 x 10^9 /L	Death
Haptoglobin	Haptoglobin	<LLN	—	Absent	—	Death
Hemoglobin	Hemoglobin	<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death
ALSO CONSIDER: Haptoglobin; Hemoglobin.						
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death
Leukocytes (total WBC)	Leukocytes	<LLN – 3000/mm^3 <LLN – 3.0 x 10^9 /L	<3000 – 2000/mm^3 <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3 <2.0 – 1.0 x 10^9 /L	<1000/mm^3 <1.0 x 10^9 /L	Death
Lymphopenia	Lymphopenia	<LLN – 800/mm^3 <LLN x 0.8 – 10^9 /L	<800 – 500/mm^3 <0.8 – 0.5 x 10^9 /L	<500 – 200 mm^3 <0.5 – 0.2 x 10^9 /L	<200/mm^3 <0.2 x 10^9 /L	Death
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts ≤5%)	RAEB or RAEB-T (marrow blasts >5%)	Death
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	<LLN – 1500/mm^3 <LLN – 1.5 x 10^9 /L	<1500 – 1000/mm^3 <1.5 – 1.0 x 10^9 /L	<1000 – 500/mm^3 <1.0 – 0.5 x 10^9 /L	<500/mm^3 <0.5 x 10^9 /L	Death
Platelets	Platelets	<LLN – 75,000/mm^3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm^3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm^3 <50.0 – 25.0 x 10^9 /L	<25,000/mm^3 <25.0 x 10^9 /L	Death
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC ARRHYTHMIA

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/ atrioventricular heart block – *Select*:	Conduction abnormality – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Asystole – AV Block-First degree – AV Block-Second degree Mobitz Type I (Wenckebach) – AV Block-Second degree Mobitz Type II – AV Block-Third degree (Complete AV block) – Conduction abnormality NOS – Sick Sinus Syndrome – Stokes-Adams Syndrome – Wolff-Parkinson-White Syndrome						
Palpitations	Palpitations	Present	Present with associated symptoms (e.g., lightheadedness, shortness of breath)	—	—	—
REMARK: Grade palpitations only in the absence of a documented arrhythmia.						
Prolonged QTc interval	Prolonged QTc	QTc >0.45 – 0.47 second	QTc >0.47 – 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	Death
Supraventricular and nodal arrhythmia – *Select*:	Supraventricular arrhythmia – *Select*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
– Atrial fibrillation – Atrial flutter – Atrial tachycardia/Paroxysmal Atrial Tachycardia – Nodal/Junctional – Sinus arrhythmia – Sinus bradycardia – Sinus tachycardia – Supraventricular arrhythmia NOS – Supraventricular extrasystoles (Premature Atrial Contractions; Premature Nodal/Junctional Contractions) – Supraventricular tachycardia						
NAVIGATION NOTE: Syncope is graded as Syncope (fainting) in the NEUROLOGY CATEGORY.						

CARDIAC ARRHYTHMIA

Page 2 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vasovagal episode	Vasovagal episode	—	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Ventricular arrhythmia – S*elect:* – Bigeminy – Idioventricular rhythm – PVCs – Torsade de pointes – Trigeminy – Ventricular arrhythmia NOS – Ventricular fibrillation – Ventricular flutter – Ventricular tachycardia	Ventricular arrhythmia – S*elect*	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Cardiac Arrhythmia – Other (Specify, __)	Cardiac Arrhythmia – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CARDIAC GENERAL

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

CARDIAC GENERAL

Page 2 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hypotension	Hypotension	Changes, intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)	Death
ALSO CONSIDER: Syncope (fainting).						
Left ventricular diastolic dysfunction	Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated	Death
Left ventricular systolic dysfunction	Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40%; SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
NAVIGATION NOTE: Myocardial infarction is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Myocarditis	Myocarditis	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	Pericardial effusion	Asymptomatic effusion	—	Effusion with physiologic consequences	Life-threatening consequences (e.g., tamponade); emergency intervention indicated	Death
Pericarditis	Pericarditis	Asymptomatic, ECG or physical exam (rub) changes consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; emergency intervention indicated	Death
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pulmonary hypertension	Pulmonary hypertension	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic hypertension, responsive to therapy	Symptomatic hypertension, poorly controlled	Death
Restrictive cardiomyopathy	Restrictive cardiomyopathy	Asymptomatic, therapy not indicated	Asymptomatic, therapy indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death

CARDIAC GENERAL						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Right ventricular dysfunction (cor pulmonale)	Right ventricular dysfunction	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale poorly controlled; intervention such as ventricular assist device, or heart transplant indicated	Death
Valvular heart disease	Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis; treatment other than endocarditis prophylaxis not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; intervention (e.g., valve replacement, valvuloplasty) indicated	Death
Cardiac General – Other (Specify, __)	Cardiac General – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

COAGULATION

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	DIC	—	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer. ALSO CONSIDER: Platelets.						
Fibrinogen	Fibrinogen	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 – <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 – <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	Death
REMARK: Use % decrease only when baseline is <LLN (local laboratory value).						
INR (International Normalized Ratio of prothrombin time)	INR	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
PTT (Partial Thromboplastin Time)	PTT	>1 – 1.5 x ULN	>1.5 – 2 x ULN	>2 x ULN	—	—
ALSO CONSIDER: Hemorrhage, CNS; Hemorrhage, GI – *Select*; Hemorrhage, GU – *Select*; Hemorrhage, pulmonary/upper respiratory – *Select.*						
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	Thrombotic microangiopathy	Evidence of RBC destruction (schistocytosis) without clinical consequences	—	Laboratory findings present with clinical consequences (e.g., renal insufficiency, petechiae)	Laboratory findings and life-threatening or disabling consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure)	Death
REMARK: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). ALSO CONSIDER: Creatinine; Hemoglobin; Platelets.						
Coagulation – Other (Specify, __)	Coagulation – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

CONSTITUTIONAL SYMPTOMS

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	Fever	38.0 – 39.0°C (100.4 – 102.2°F)	>39.0 – 40.0°C (102.3 – 104.0°F)	>40.0°C (>104.0°F) for ≤24 hrs	>40.0°C (>104.0°F) for >24 hrs	Death
REMARK: The temperature measurements listed are oral or tympanic.						
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
NAVIGATION NOTE: Hot flashes are graded as Hot flashes/flushes in the ENDOCRINE CATEGORY.						
Hypothermia	Hypothermia	—	35 – >32°C 95 – >89.6°F	32 – >28°C 89.6 – >82.4° F	≤28 °C 82.4°F or life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Insomnia	Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping, interfering with function but not interfering with ADL	Frequent difficulty sleeping, interfering with ADL	Disabling	—
REMARK: If pain or other symptoms interfere with sleep, do NOT grade as insomnia. Grade primary event(s) causing insomnia.						
Obesity[2]	Obesity	—	BMI 25 – 29.9 kg/m^2	BMI 30 – 39.99 kg/m^2	BMI ≥40 kg/m^2	—
REMARK: BMI = (weight [kg]) / (height [m])^2						
Odor (patient odor)	Patient odor	Mild odor	Pronounced odor	—	—	—
Rigors/chills	Rigors/chills	Mild	Moderate, narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—

[2] NHLBI Obesity Task Force. "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," *The Evidence Report,* Obes Res 6:51S-209S, 1998.

CONSTITUTIONAL SYMPTOMS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Sweating (diaphoresis)	Sweating	Mild and occasional	Frequent or drenching	—	—	—
ALSO CONSIDER: Hot flashes/flushes.						
Weight gain	Weight gain	5 – <10% of baseline	10 – <20% of baseline	≥20% of baseline	—	—
REMARK: Edema, depending on etiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.						
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).						
Weight loss	Weight loss	5 to <10% from baseline; intervention not indicated	10 – <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	—	—
Constitutional Symptoms – Other (Specify, __)	Constitutional Symptoms – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

DEATH

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Death not associated with CTCAE term – *Select*: – Death NOS – Disease progression NOS – Multi-organ failure – Sudden death	Death not associated with CTCAE term – *Select*	—	—	—	—	Death

REMARK: Grade 5 is the only appropriate grade. 'Death not associated with CTCAE term – *Select'* is to be used where a death:

1. Cannot be attributed to a CTCAE term associated with Grade 5.
2. Cannot be reported within any CATEGORY using a CTCAE 'Other (Specify, __)'.

DERMATOLOGY/SKIN

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Atrophy, skin	Atrophy, skin	Detectable	Marked	—	—	—
Atrophy, subcutaneous fat	Atrophy, subcutaneous fat	Detectable	Marked	—	—	—
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue).						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Bruising	Localized or in a dependent area	Generalized	—	—	—
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						
Cheilitis	Cheilitis	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	—	—
Dry skin	Dry skin	Asymptomatic	Symptomatic, not interfering with ADL	Interfering with ADL	—	—
Flushing	Flushing	Asymptomatic	Symptomatic	—	—	—
Hair loss/alopecia (scalp or body)	Alopecia	Thinning or patchy	Complete	—	—	—
Hyperpigmentation	Hyperpigmentation	Slight or localized	Marked or generalized	—	—	—
Hypopigmentation	Hypopigmentation	Slight or localized	Marked or generalized	—	—	—
Induration/fibrosis (skin and subcutaneous tissue)	Induration	Increased density on palpation	Moderate impairment of function not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	—	—
ALSO CONSIDER: Fibrosis-cosmesis; Fibrosis-deep connective tissue.						
Injection site reaction/ extravasation changes	Injection site reaction	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration.						

DERMATOLOGY/SKIN						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

DERMATOLOGY/SKIN						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Skin breakdown/ decubitus ulcer	Decubitus	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
REMARK: Skin breakdown/decubitus ulcer is to be used for loss of skin integrity or decubitus ulcer from pressure or as the result of operative or medical intervention.						
Striae	Striae	Mild	Cosmetically significant	—	—	—
Telangiectasia	Telangiectasia	Few	Moderate number	Many and confluent	—	—
Ulceration	Ulceration	—	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)	Death
Urticaria (hives, welts, wheals)	Urticaria	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for ≥24 hrs	—	—
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
Wound complication, non-infectious	Wound complication, non-infectious	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia	Symptomatic hernia without evidence of strangulation; fascial disruption/dehiscence without evisceration; primary wound closure or revision by operative intervention indicated; hospitalization or hyperbaric oxygen indicated	Symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
REMARK: Wound complication, non-infectious is to be used for separation of incision, hernia, dehiscence, evisceration, or second surgery for wound revision.						
Dermatology/Skin – Other (Specify, __)	Dermatology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ENDOCRINE						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
REMARK: Adrenal insufficiency includes any of the following signs and symptoms: abdominal pain, anorexia, constipation, diarrhea, hypotension, pigmentation of mucous membranes, pigmentation of skin, salt craving, syncope (fainting), vitiligo, vomiting, weakness, weight loss. Adrenal insufficiency must be confirmed by laboratory studies (low cortisol frequently accompanied by low aldosterone). ALSO CONSIDER: Potassium, serum-high (hyperkalemia); Thyroid function, low (hypothyroidism).						
Cushingoid appearance (e.g., moon face, buffalo hump, centripetal obesity, cutaneous striae)	Cushingoid	—	Present	—	—	—
ALSO CONSIDER: Glucose, serum-high (hyperglycemia); Potassium, serum-low (hypokalemia).						
Feminization of male	Feminization of male	—	—	Present	—	—
NAVIGATION NOTE: Gynecomastia is graded in the SEXUAL/REPRODUCTIVE FUNCTION CATEGORY.						
Hot flashes/flushes[3]	Hot flashes	Mild	Moderate	Interfering with ADL	—	—
Masculinization of female	Masculinization of female	—	—	Present	—	—
Neuroendocrine: ACTH deficiency	ACTH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., severe hypotension)	Death
Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH)	ADH	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences	Death
Neuroendocrine: gonadotropin secretion abnormality	Gonadotropin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; osteopenia; fracture; infertility	—	—
Neuroendocrine: growth hormone secretion abnormality	Growth hormone	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	—	—	—
Neuroendocrine: prolactin hormone secretion abnormality	Prolactin	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL; amenorrhea; galactorrhea	—	Death

[3] Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl HJ, "Methodologic Lessons Learned from Hot Flash Studies," *J Clin Oncol* 2001 Dec 1;19(23):4280-90

ENDOCRINE						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pancreatic endocrine: glucose intolerance	Diabetes	Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)	Death
Parathyroid function, low (hypoparathyroidism)	Hypoparathyroidism	Asymptomatic, intervention not indicated	Symptomatic; intervention indicated	—	—	—
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Hyperthyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid suppression therapy indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening consequences (e.g., thyroid storm)	Death
Thyroid function, low (hypothyroidism)	Hypothyroidism	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL; thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Endocrine – Other (Specify, __)	Endocrine – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GASTROINTESTINAL						Page 1 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – *Select* in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALSO CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
ALSO CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

GASTROINTESTINAL

Page 2 of 10

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – *Select*.						

GASTROINTESTINAL

Page 3 of 10

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow. ALSO CONSIDER: Salivary gland changes/saliva.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – *Select*. ALSO CONSIDER: Dehydration; Esophagitis.						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Esophagitis includes reflux esophagitis. ALSO CONSIDER: Dysphagia (difficulty swallowing).						

GASTROINTESTINAL						Page 4 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fistula, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – *Select*	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Ulcer, GI – *Select*.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

GASTROINTESTINAL

Page 5 of 10

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying). ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – *Select*; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – *Select*: – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anasomotic), GI – *Select* is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death

GASTROINTESTINAL						Page 6 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Mucositis/stomatitis (clinical exam) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – *Select*	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – *Select*: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/ symptomatic) – *Select*	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

GASTROINTESTINAL						Page 7 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Necrosis, GI – *Select*: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – *Select*	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
ALSO CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – *Select*: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						

GASTROINTESTINAL						Page 8 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Perforation, GI – *Select*: – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – *Select*	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Obstruction, GI – *Select;* Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select*.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – *Select* in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – *Select*; Mucositis/stomatitis (functional/symptomatic) – *Select*; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

GASTROINTESTINAL						Page 9 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GI – *Select*: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – *Select*	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death
ALSO CONSIDER: Colitis; Hemorrhage, GI – *Select* ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).						

GASTROINTESTINAL						Page 10 of 10
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Ulcer, GI – *Select*: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*.						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

GROWTH AND DEVELOPMENT

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bone age (alteration in bone age)	Bone age	—	±2 SD (standard deviation) from normal	—	—	—
Bone growth: femoral head; slipped capital femoral epiphysis	Femoral head growth	Mild valgus/varus deformity	Moderate valgus/varus deformity, symptomatic, interfering with function but not interfering with ADL	Mild slipped capital femoral epiphysis; operative intervention (e.g., fixation) indicated; interfering with ADL	Disabling; severe slipped capital femoral epiphysis >60%; avascular necrosis	—
Bone growth: limb length discrepancy	Limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 – 5 cm; shoe lift indicated	Severe length discrepancy >5 cm; operative intervention indicated; interfering with ADL	Disabling; epiphysiodesis	—
Bone growth: spine kyphosis/lordosis	Kyphosis/lordosis	Mild radiographic changes	Moderate accentuation; interfering with function but not interfering with ADL	Severe accentuation; operative intervention indicated; interfering with ADL	Disabling (e.g., cannot lift head)	—
Growth velocity (reduction in growth velocity)	Reduction in growth velocity	10 – 29% reduction in growth from the baseline growth curve	30 – 49% reduction in growth from the baseline growth curve	≥50% reduction in growth from the baseline growth curve	—	—
Puberty (delayed)	Delayed puberty	—	No breast development by age 13 yrs for females; no Tanner Stage 2 development by age 14.5 yrs for males	No sexual development by age 14 yrs for girls, age 16 yrs for boys; hormone replacement indicated	—	—
REMARK: Do not use testicular size for Tanner Stage in male cancer survivors.						
Puberty (precocious)	Precocious puberty	—	Physical signs of puberty <7 years for females, <9 years for males	—	—	—
Short stature	Short stature	Beyond two standard deviations of age and gender mean height	Altered ADL	—	—	—
REMARK: Short stature is secondary to growth hormone deficiency. ALSO CONSIDER: Neuroendocrine: growth hormone secretion abnormality.						
Growth and Development – Other (Specify, __)	Growth and Development – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

HEMORRHAGE/BLEEDING

Page 1 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage/bleeding associated with surgery, intra-operative or postoperative	Hemorrhage with surgery	—	—	Requiring transfusion of 2 units non-autologous (10 cc/kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death
REMARK: Postoperative period is defined as ≤72 hours after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability	Death
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING

Page 2 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GI – *Select*: – Abdomen NOS – Anus – Biliary tree – Cecum/appendix – Colon – Duodenum – Esophagus – Ileum – Jejunum – Liver – Lower GI NOS – Oral cavity – Pancreas – Peritoneal cavity – Rectum – Stoma – Stomach – Upper GI NOS – Varices (esophageal) – Varices (rectal)	Hemorrhage, GI – *Select*	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death

REMARK: Transfusion implies pRBC.

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).

HEMORRHAGE/BLEEDING

Page 3 of 4

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Hemorrhage, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Retroperitoneum – Spermatic cord – Stoma – Testes – Ureter – Urethra – Urinary NOS – Uterus – Vagina – Vas deferens	Hemorrhage, GU – *Select*	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Hemorrhage, pulmonary/ upper respiratory – *Select*: – Bronchopulmonary NOS – Bronchus – Larynx – Lung – Mediastinum – Nose – Pharynx – Pleura – Respiratory tract NOS – Stoma – Trachea	Hemorrhage pulmonary – *Select*	Mild, intervention not indicated	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated	Death
REMARK: Transfusion implies pRBC. ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	—	—
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PTT (Partial Thromboplastin Time).						

HEMORRHAGE/BLEEDING						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Vitreous hemorrhage is graded in the OCULAR/VISUAL CATEGORY.						
Hemorrhage/Bleeding – Other (Specify, __)	Hemorrhage – Other (Specify)	Mild without transfusion	—	Transfusion indicated	Catastrophic bleeding, requiring major non-elective intervention	Death

HEPATOBILIARY/PANCREAS

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Biliary tree damage is graded as Fistula, GI – *Select*; Leak (including anastomotic), GI – *Select*; Necrosis, GI – *Select*; Obstruction, GI – *Select*; Perforation, GI – *Select*; Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Cholecystitis	Cholecystitis	Asymptomatic, radiographic findings only	Symptomatic, medical intervention indicated	Interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*.						
Liver dysfunction/failure (clinical)	Liver dysfunction	—	Jaundice	Asterixis	Encephalopathy or coma	Death
REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin. ALSO CONSIDER: Bilirubin (hyperbilirubinemia).						
Pancreas, exocrine enzyme deficiency	Pancreas, exocrine enzyme deficiency	—	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening consequences	Death
ALSO CONSIDER: Diarrhea.						
Pancreatitis	Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)	Death
ALSO CONSIDER: Amylase.						
NAVIGATION NOTE: Stricture (biliary tree, hepatic or pancreatic) is graded as Stricture/stenosis (including anastomotic), GI – *Select* in the GASTROINTESTINAL CATEGORY.						
Hepatobiliary/Pancreas – Other (Specify, __)	Hepatobiliary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Colitis, infectious (e.g., Clostridium difficile)	Colitis, infectious	Asymptomatic, pathologic or radiographic findings only	Abdominal pain with mucus and/or blood in stool	IV antibiotics or TPN indicated	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis or toxic megacolon); operative resection or diversion indicated	Death
ALSO CONSIDER: Hemorrhage, GI – *Select*; Typhlitis (cecal inflammation).						
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10^9/L, fever ≥38.5°C)	Febrile neutropenia	—	—	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection (documented clinically) with Grade 3 or 4 ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Fever with Grade 3 or 4 neutrophils in the absence of documented infection is graded as Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection). ALSO CONSIDER: Neutrophils/granulocytes (ANC/AGC).						
Infection with normal ANC or Grade 1 or 2 neutrophils – *Select* '*Select*' AEs appear at the end of the CATEGORY.	Infection with normal ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death

INFECTION						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Infection with unknown ANC – *Select* *'Select'* AEs appear at the end of the CATEGORY.	Infection with unknown ANC – *Select*	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
REMARK: Infection with unknown ANC – *Select* is to be used in the rare case when ANC is unknown.						
Opportunistic infection associated with ≥Grade 2 Lymphopenia	Opportunistic infection	—	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
ALSO CONSIDER: Lymphopenia.						
Viral hepatitis	Viral hepatitis	Present; transaminases and liver function normal	Transaminases abnormal, liver function normal	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
REMARK: Non-viral hepatitis is graded as Infection – *Select*. ALSO CONSIDER: Albumin, serum-low (hypoalbuminemia); ALT, SGPT (serum glutamic pyruvic transaminase); AST, SGOT (serum glutamic oxaloacetic transaminase); Bilirubin (hyperbilirubinemia); Encephalopathy.						
Infection – Other (Specify, __)	Infection – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

INFECTION – *SELECT*

Page 3 of 3

AUDITORY/EAR
- External ear (otitis externa)
- Middle ear (otitis media)

CARDIOVASCULAR
- Artery
- Heart (endocarditis)
- Spleen
- Vein

DERMATOLOGY/SKIN
- Lip/perioral
- Peristomal
- Skin (cellulitis)
- Ungual (nails)

GASTROINTESTINAL
- Abdomen NOS
- Anal/perianal
- Appendix
- Cecum
- Colon
- Dental-tooth
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral cavity-gums (gingivitis)
- Peritoneal cavity
- Rectum
- Salivary gland
- Small bowel NOS
- Stomach

GENERAL
- Blood
- Catheter-related
- Foreign body (e.g., graft, implant, prosthesis, stent)
- Wound

HEPATOBILIARY/PANCREAS
- Biliary tree
- Gallbladder (cholecystitis)
- Liver
- Pancreas

LYMPHATIC
- Lymphatic

MUSCULOSKELETAL
- Bone (osteomyelitis)
- Joint
- Muscle (infection myositis)
- Soft tissue NOS

NEUROLOGY
- Brain (encephalitis, infectious)
- Brain + Spinal cord (encephalomyelitis)
- Meninges (meningitis)
- Nerve-cranial
- Nerve-peripheral
- Spinal cord (myelitis)

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Larynx
- Lung (pneumonia)
- Mediastinum NOS
- Mucosa
- Neck NOS
- Nose
- Paranasal
- Pharynx
- Pleura (empyema)
- Sinus
- Trachea
- Upper aerodigestive NOS
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder (urinary)
- Kidney
- Prostate
- Ureter
- Urethra
- Urinary tract NOS

SEXUAL/REPRODUCTIVE FUNCTION
- Cervix
- Fallopian tube
- Pelvis NOS
- Penis
- Scrotum
- Uterus
- Vagina
- Vulva

LYMPHATICS

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
ALSO CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphedema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphedema refers to changes due to venous stasis. ALSO CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

LYMPHATICS						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting ≥40% of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolymphatic cording	Phlebolymphatic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

METABOLIC/LABORATORY

Page 1 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acidosis (metabolic or respiratory)	Acidosis	pH <normal, but ≥7.3	—	pH <7.3	pH <7.3 with life-threatening consequences	Death
Albumin, serum-low (hypoalbuminemia)	Hypoalbuminemia	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	—	Death
Alkaline phosphatase	Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Alkalosis (metabolic or respiratory)	Alkalosis	pH >normal, but ≤7.5	—	pH >7.5	pH >7.5 with life-threatening consequences	Death
ALT, SGPT (serum glutamic pyruvic transaminase)	ALT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Amylase	Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
AST, SGOT (serum glutamic oxaloacetic transaminase)	AST	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Bicarbonate, serum-low	Bicarbonate, serum-low	<LLN – 16 mmol/L	<16 – 11 mmol/L	<11 – 8 mmol/L	<8 mmol/L	Death
Bilirubin (hyperbilirubinemia)	Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
REMARK: Jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.						
Calcium, serum-low (hypocalcemia)	Hypocalcemia	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L Ionized calcium: <0.8 mmol/L	Death
REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin is <4.0 g/dL, hypocalcemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) – 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.						

[4]Crit Rev Clin Lab Sci 1984;21(1):51-97

METABOLIC/LABORATORY						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death
REMARK: Adjust to age-appropriate levels for pediatric patients. ALSO CONSIDER: Glomerular filtration rate.						
GGT (γ-Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Creatinine.						
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.						
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium, serum-high (hypermagnesemia)	Hypermagnesemia	>ULN – 3.0 mg/dL >ULN – 1.23 mmol/L	—	>3.0 – 8.0 mg/dL >1.23 – 3.30 mmol/L	>8.0 mg/dL >3.30 mmol/L	Death
Magnesium, serum-low (hypomagnesemia)	Hypomagnesemia	<LLN – 1.2 mg/dL <LLN – 0.5 mmol/L	<1.2 – 0.9 mg/dL <0.5 – 0.4 mmol/L	<0.9 – 0.7 mg/dL <0.4 – 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death
Phosphate, serum-low (hypophosphatemia)	Hypophosphatemia	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L	Death
Potassium, serum-high (hyperkalemia)	Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death

METABOLIC/LABORATORY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Potassium, serum-low (hypokalemia)	Hypokalemia	<LLN – 3.0 mmol/L	—	<3.0 – 2.5 mmol/L	<2.5 mmol/L	Death
Proteinuria	Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome	Death
Sodium, serum-high (hypernatremia)	Hypernatremia	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
Sodium, serum-low (hyponatremia)	Hyponatremia	<LLN – 130 mmol/L	—	<130 – 120 mmol/L	<120 mmol/L	Death
Triglyceride, serum-high (hypertriglyceridemia)	Hypertriglyceridemia	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10 x ULN	>10 x ULN	Death
Uric acid, serum-high (hyperuricemia)	Hyperuricemia	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	—	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia); Renal failure; Tumor lysis syndrome.						
Metabolic/Laboratory – Other (Specify, __)	Metabolic/Lab – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 1 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Arthritis (non-septic)	Arthritis	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL	Disabling	Death
REMARK: Report only when the diagnosis of arthritis (e.g., inflammation of a joint or a state characterized by inflammation of joints) is made. Arthralgia (sign or symptom of pain in a joint, especially non-inflammatory in character) is graded as Pain – *Select* in the PAIN CATEGORY.						
Bone: spine-scoliosis	Scoliosis	≤20 degrees; clinically undetectable	>20 – 45 degrees; visible by forward flexion; interfering with function but not interfering with ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; interfering with ADL	Disabling (e.g., interfering with cardiopulmonary function)	Death
Cervical spine-range of motion	Cervical spine ROM	Mild restriction of rotation or flexion between 60 – 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	—	—
REMARK: 60 – 65 degrees of rotation is required for reversing a car; 60 – 65 degrees of flexion is required to tie shoes.						
Exostosis	Exostosis	Asymptomatic	Involving multiple sites; pain or interfering with function	Excision indicated	Progression to malignancy (i.e., chondrosarcoma)	Death
Extremity-lower (gait/walking)	Gait/walking	Limp evident only to trained observer and able to walk ≥1 kilometer; cane indicated for walking	Noticeable limp, or limitation of limb function, but able to walk ≥0.1 kilometer (1 city block); quad cane indicated for walking	Severe limp with stride modified to maintain balance (widened base of support, marked reduction in step length); ambulation limited to walker; crutches indicated	Unable to walk	—
ALSO CONSIDER: Ataxia (incoordination); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*.						
Extremity-upper (function)	Extremity-upper (function)	Able to perform most household or work activities with affected limb	Able to perform most household or work activities with compensation from unaffected limb	Interfering with ADL	Disabling; no function of affected limb	—
Fibrosis-cosmesis	Fibrosis-cosmesis	Visible only on close examination	Readily apparent but not disfiguring	Significant disfigurement; operative intervention indicated if patient chooses	—	—

MUSCULOSKELETAL/SOFT TISSUE						Page 2 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
ALSO CONSIDER: Induration/fibrosis (skin and subcutaneous tissue); Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*; Neuropathy: motor; Neuropathy: sensory.						
Fracture	Fracture	Asymptomatic, radiographic findings only (e.g., asymptomatic rib fracture on plain x-ray, pelvic insufficiency fracture on MRI, etc.)	Symptomatic but non-displaced; immobilization indicated	Symptomatic and displaced or open wound with bone exposure; operative intervention indicated	Disabling; amputation indicated	Death
Joint-effusion	Joint-effusion	Asymptomatic, clinical or radiographic findings only	Symptomatic; interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	Death
ALSO CONSIDER: Arthritis (non-septic).						
Joint-function[5]	Joint-function	Stiffness interfering with athletic activity; ≤25% loss of range of motion (ROM)	Stiffness interfering with function but not interfering with ADL; >25 – 50% decrease in ROM	Stiffness interfering with ADL; >50 – 75% decrease in ROM	Fixed or non-functional joint (arthrodesis); >75% decrease in ROM	—
ALSO CONSIDER: Arthritis (non-septic).						
Local complication – device/prosthesis-related	Device/prosthesis	Asymptomatic	Symptomatic, but not interfering with ADL; local wound care; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated (e.g., hardware/device replacement or removal, reconstruction)	Life-threatening; disabling; loss of limb or organ	Death
Lumbar spine-range of motion	Lumbar spine ROM	Stiffness and difficulty bending to the floor to pick up a very light object but able to do activity	Some lumbar spine flexion but requires a reaching aid to pick up a very light object from the floor	Ankylosed/fused over multiple segments with no L-spine flexion (i.e., unable to reach to floor to pick up a very light	—	—

[5] Adapted from the *International SFTR Method of Measuring and Recording Joint Motion, International Standard Orthopedic Measurements (ISOM),* Jon J. Gerhardt and Otto A. Russee, Bern, Switzerland, Han Huber 9 Publisher), 1975.

MUSCULOSKELETAL/SOFT TISSUE Page 3 of 4						
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				object)		
Muscle weakness, generalized or specific area (not due to neuropathy) – *Select*: – Extraocular – Extremity-lower – Extremity-upper – Facial – Left-sided – Ocular – Pelvic – Right-sided – Trunk – Whole body/generalized	Muscle weakness – *Select*	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
ALSO CONSIDER: Fatigue (asthenia, lethargy, malaise).						
Muscular/skeletal hypoplasia	Muscular/skeletal hypoplasia	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Functionally significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing	Disabling	—
Myositis (inflammation/damage of muscle)	Myositis	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
REMARK: Myositis implies muscle damage (i.e., elevated CPK). ALSO CONSIDER: CPK (creatine phosphokinase); Pain – *Select*.						
Osteonecrosis (avascular necrosis)	Osteonecrosis	Asymptomatic, radiographic findings only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Disabling	Death

MUSCULOSKELETAL/SOFT TISSUE						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Osteoporosis[6]	Osteoporosis	Radiographic evidence of osteoporosis or Bone Mineral Density (BMD) t-score –1 to –2.5 (osteopenia) and no loss of height or therapy indicated	BMD t-score < –2.5; loss of height <2 cm; anti-osteoporotic therapy indicated	Fractures; loss of height ≥2 cm	Disabling	Death
Seroma	Seroma	Asymptomatic	Symptomatic; medical intervention or simple aspiration indicated	Symptomatic, interventional radiology or operative intervention indicated	—	—
Soft tissue necrosis – *Select*: – Abdomen – Extremity-lower – Extremity-upper – Head – Neck – Pelvic – Thorax	Soft tissue necrosis – *Select*	—	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Death
Trismus (difficulty, restriction or pain when opening mouth)	Trismus	Decreased range of motion without impaired eating	Decreased range of motion requiring small bites, soft foods or purees	Decreased range of motion with inability to adequately aliment or hydrate orally	—	—
NAVIGATION NOTE: Wound-infectious is graded as Infection – *Select* in the INFECTION CATEGORY.						
NAVIGATION NOTE: Wound non-infectious is graded as Wound complication, non-infectious in the DERMATOLOGY/SKIN CATEGORY.						
Musculoskeletal/Soft Tissue – Other (Specify, __)	Musculoskeletal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

[6] "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis," Report of a *WHO Study Group Technical Report Series*, No. 843, 1994, v + 129 pages [C*, E, F, R, S], ISBN 92 4 120843 0, Sw.fr. 22.-/US $19.80; in developing countries: Sw.fr. 15.40, Order no. 1100843

NEUROLOGY						Page 1 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: ADD (Attention Deficit Disorder) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea) interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling (e.g., paraplegia)	Death
ALSO CONSIDER: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling	Death
REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs	Death
NAVIGATION NOTE: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the HEMORRHAGE/BLEEDING CATEGORY.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL; medical intervention indicated	Symptomatic and interfering with ADL; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated	Death
REMARK: Cognitive disturbance may be used for Attention Deficit Disorder (ADD).						

NEUROLOGY						Page 2 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL	Confusion or delirium interfering with ADL	Harmful to others or self; hospitalization indicated	Death
REMARK: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
NAVIGATION NOTE: Cranial neuropathy is graded as Neuropathy-cranial – *Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabling	—
REMARK: Dizziness includes disequilibrium, lightheadedness, and vertigo. ALSO CONSIDER: Neuropathy: cranial – *Select*; Syncope (fainting).						
NAVIGATION NOTE: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
ALSO CONSIDER: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration – *Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/ involuntary movement/ restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary movements or torticollis interfering with ADL	Disabling	Death
NAVIGATION NOTE: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) is graded as Pain – *Select* in the PAIN CATEGORY.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADL	Severe symptoms or neurological deficit interfering with ADL	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death

NEUROLOGY						Page 3 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADL; blood patch indicated	Symptomatic, interfering with ADL; operative intervention indicated	Life-threatening; disabling	Death
REMARK: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT)	—	—
REMARK: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunas, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADL	Memory impairment interfering with ADL	Amnesia	—
Mental status[7]	Mental status	—	1 – 3 point below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 point below age and educational norm in Folstein MMSE	—	—
Mood alteration – *Select*: – Agitation – Anxiety – Depression – Euphoria	Mood alteration – *Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or others	Death
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADL	Weakness or sensory loss interfering with ADL	Disabling	Death

[7] Folstein MF, Folstein, SE and McHugh PR (1975) "Mini-Mental State: A Practical Method for Grading the State of Patients for the Clinician," *Journal of Psychiatric Research*, 12: 189-198

NEUROLOGY							Page 4 of 5
		Grade					
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**	
NAVIGATION NOTE: Neuropathic pain is graded as Pain – *Select* in the PAIN CATEGORY.							
Neuropathy: cranial – *Select*: – CN I Smell – CN II Vision – CN III Pupil, upper eyelid, extra ocular movements – CN IV Downward, inward movement of eye – CN V Motor-jaw muscles; Sensory-facial – CN VI Lateral deviation of eye – CN VII Motor-face; Sensory-taste – CN VIII Hearing and balance – CN IX Motor-pharynx; Sensory-ear, pharynx, tongue – CN X Motor-palate; pharynx, larynx – CN XI Motor-sternomastoid and trapezius – CN XII Motor-tongue	Neuropathy: cranial – *Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death	
Neuropathy: motor	Neuropathy-motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death	
REMARK: Cranial nerve motor neuropathy is graded as Neuropathy: cranial – *Select*. ALSO CONSIDER: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.							
Neuropathy: sensory	Neuropathy-sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death	
REMARK: Cranial nerve sensory neuropathy is graded as Neuropathy: cranial – *Select*.							
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death	
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADL; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death	
Psychosis (hallucinations/ delusions)	Psychosis	—	Transient episode	Interfering with ADL; medication, supervision	Harmful to others or self; life-threatening	Death	

NEUROLOGY						Page 5 of 5
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
				or restraints indicated	consequences	
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADL	Interfering with ADL	Disabling; paralysis	Death
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
REMARK: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction. ALSO CONSIDER: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
ALSO CONSIDER: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block – *Select*; Dizziness; Supraventricular and nodal arrhythmia – *Select*; Vasovagal episode; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the GASTROINTESTINAL CATEGORY.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	—
Neurology – Other (Specify, __)	Neurology – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

OCULAR/VISUAL						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Cataract	Cataract	Asymptomatic, detected on exam only	Symptomatic, with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	—	—
Dry eye syndrome	Dry eye	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	—	—
Eyelid dysfunction	Eyelid dysfunction	Asymptomatic	Symptomatic, interfering with function but not ADL; requiring topical agents or epilation	Symptomatic; interfering with ADL; surgical intervention indicated	—	—
REMARK: Eyelid dysfunction includes canalicular stenosis, ectropion, entropion, erythema, madarosis, symblepharon, telangiectasis, thickening, and trichiasis. ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Glaucoma	Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficit (i.e., nasal step or arcuate deficit); multiple topical or oral agents indicated	EIOP causing marked visual field deficits (i.e., involving both superior and inferior visual fields); operative intervention indicated	EIOP resulting in blindness (20/200 or worse); enucleation indicated	—
Keratitis (corneal inflammation/corneal ulceration)	Keratitis	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness (20/200 or worse)	—
NAVIGATION NOTE: Ocular muscle weakness is graded as Muscle weakness, generalized or specific area (not due to neuropathy) – *Select* in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Night blindness (nyctalopia)	Nyctalopia	Symptomatic, not interfering with function	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—

OCULAR/VISUAL						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nystagmus	Nystagmus	Asymptomatic	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*; Ophthalmoplegia/diplopia (double vision).						
Ocular surface disease	Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; topical antibiotics or other topical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	—	—
REMARK: Ocular surface disease includes conjunctivitis, keratoconjunctivitis sicca, chemosis, keratinization, and palpebral conjunctival epithelial metaplasia.						
Ophthalmoplegia/ diplopia (double vision)	Diplopia	Intermittently symptomatic, intervention not indicated	Symptomatic and interfering with function but not interfering with ADL	Symptomatic and interfering with ADL; surgical intervention indicated	Disabling	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Optic disc edema	Optic disc edema	Asymptomatic	Decreased visual acuity (20/40 or better); visual field defect present	Decreased visual acuity (worse than 20/40); marked visual field defect but sparing the central 20 degrees	Blindness (20/200 or worse)	—
ALSO CONSIDER: Neuropathy: cranial – *Select*.						
Proptosis/enophthalmos	Proptosis/enophthalmos	Asymptomatic, intervention not indicated	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	—	—
Retinal detachment	Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and visual acuity 20/40 or better but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness (20/200 or worse)	—
Retinopathy	Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse)	—

OCULAR/VISUAL						Page 3 of 3
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Scleral necrosis/melt	Scleral necrosis	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not interfering with ADL; moderate decrease in visual acuity (20/40 or better); medical intervention indicated	Symptomatic, interfering with ADL; marked decrease in visual acuity (worse than 20/40); operative intervention indicated	Blindness (20/200 or worse); painful eye with enucleation indicated	—
Uveitis	Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness (20/200 or worse)	—
Vision-blurred vision	Blurred vision	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-flashing lights/floaters	Flashing lights	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vision-photophobia	Photophobia	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	—
Vitreous hemorrhage	Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; vitrectomy indicated	—	—
Watery eye (epiphora, tearing)	Watery eye	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL	Symptomatic, interfering with ADL	—	—
Ocular/Visual – Other (Specify, __)	Ocular – Other (Specify)	Symptomatic not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Blindness (20/200 or worse)	Death

PAIN

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Pain – *Select*: '*Select*' AEs appear at the end of the CATEGORY.	Pain – *Select*	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—

PAIN – *SELECT*

AUDITORY/EAR
- External ear
- Middle ear

CARDIOVASCULAR
- Cardiac/heart
- Pericardium

DERMATOLOGY/SKIN
- Face
- Lip
- Oral-gums
- Scalp
- Skin

GASTROINTESTINAL
- Abdomen NOS
- Anus
- Dental/teeth/peridontal
- Esophagus
- Oral cavity
- Peritoneum
- Rectum
- Stomach

GENERAL
- Pain NOS
- Tumor pain

HEPATOBILIARY/PANCREAS
- Gallbladder
- Liver

LYMPHATIC
- Lymph node

MUSCULOSKELETAL
- Back
- Bone
- Buttock
- Extremity-limb
- Intestine
- Joint
- Muscle
- Neck
- Phantom (pain associated with missing limb)

NEUROLOGY
- Head/headache
- Neuralgia/peripheral nerve

OCULAR
- Eye

PULMONARY/UPPER RESPIRATORY
- Chest wall
- Chest/thorax NOS

PULMONARY/UPPER RESPIRATORY (*continued*)
- Larynx
- Pleura
- Sinus
- Throat/pharynx/larynx

RENAL/GENITOURINARY
- Bladder
- Kidney

SEXUAL/REPRODUCTIVE FUNCTION
- Breast
- Ovulatory
- Pelvis
- Penis
- Perineum
- Prostate
- Scrotum
- Testicle
- Urethra
- Uterus
- Vagina

PULMONARY/UPPER RESPIRATORY						Page 1 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Adult Respiratory Distress Syndrome (ARDS)	ARDS	—	—	Present, intubation not indicated	Present, intubation indicated	Death
ALSO CONSIDER: Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates.						
Aspiration	Aspiration	Asymptomatic ("silent aspiration"); endoscopy or radiographic (e.g., barium swallow) findings	Symptomatic (e.g., altered eating habits, coughing or choking episodes consistent with aspiration); medical intervention indicated (e.g., antibiotics, suction or oxygen)	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening (e.g., aspiration pneumonia or pneumonitis)	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select;* Laryngeal nerve dysfunction; Neuropathy: cranial – *Select*; Pneumonitis/pulmonary infiltrates.						
Atelectasis	Atelectasis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopic suctioning, chest physiotherapy, suctioning)	Operative (e.g., stent, laser) intervention indicated	Life-threatening respiratory compromise	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Obstruction/stenosis of airway – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Bronchospasm, wheezing	Bronchospasm	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Dyspnea (shortness of breath).						
Carbon monoxide diffusion capacity (DL_{CO})	DL_{CO}	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
ALSO CONSIDER: Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Chylothorax	Chylothorax	Asymptomatic	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening (e.g., hemodynamic instability or ventilatory support indicated)	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	—	—

PULMONARY/UPPER RESPIRATORY						Page 2 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Dyspnea (shortness of breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
ALSO CONSIDER: Hypoxia; Neuropathy: motor; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Edema, larynx	Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening airway compromise; tracheotomy, intubation, or laryngectomy indicated	Death
ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).						
FEV_1	FEV_1	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted	Death
Fistula, pulmonary/upper respiratory – *Select*: – Bronchus – Larynx – Lung – Oral cavity – Pharynx – Pleura – Trachea	Fistula, pulmonary – *Select*	Asymptomatic, radiographic findings only	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic (e.g., stent) or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have arisen. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer should be graded as Fistula, GI – esophagus in the GASTROINTESTINAL CATEGORY.						
NAVIGATION NOTE: Hemoptysis is graded as Hemorrhage, pulmonary/upper respiratory – *Select* in the HEMORRHAGE/BLEEDING CATEGORY.						
Hiccoughs (hiccups, singultus)	Hiccoughs	Symptomatic, intervention not indicated	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL	—	—
Hypoxia	Hypoxia	—	Decreased O_2 saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased O_2 saturation at rest; continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death

PULMONARY/UPPER RESPIRATORY						Page 3 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nasal cavity/paranasal sinus reactions	Nasal/paranasal reactions	Asymptomatic mucosal crusting, blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow	Stenosis with significant nasal obstruction; interfering with ADL	Necrosis of soft tissue or bone	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
Obstruction/stenosis of airway – *Select*: – Bronchus – Larynx – Pharynx – Trachea	Airway obstruction – *Select*	Asymptomatic obstruction or stenosis on exam, endoscopy, or radiograph	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Interfering with ADL; stridor or endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; tracheotomy or intubation indicated	Death
Pleural effusion (non-malignant)	Pleural effusion	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g., causing hemodynamic instability or ventilatory support indicated)	Death
ALSO CONSIDER: Atelectasis; Cough; Dyspnea (shortness of breath); Hypoxia; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
NAVIGATION NOTE: Pleuritic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
Pneumonitis/pulmonary infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*; Pneumonitis/pulmonary infiltrates; Pulmonary fibrosis (radiographic changes).						
Pneumothorax	Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; intervention indicated (e.g., hospitalization for observation, tube placement without sclerosis)	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability (e.g., tension pneumothorax); ventilatory support indicated	Death
Prolonged chest tube drainage or air leak after pulmonary resection	Chest tube drainage or leak	—	Sclerosis or additional tube thoracostomy indicated	Operative intervention indicated (e.g., thoracotomy with stapling or sealant application)	Life-threatening; debilitating; organ resection indicated	Death

PULMONARY/UPPER RESPIRATORY						Page 4 of 4
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Prolonged intubation after pulmonary resection (>24 hrs after surgery)	Prolonged intubation	—	Extubated within 24 – 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Tracheostomy indicated	Death
NAVIGATION NOTE: Pulmonary embolism is graded as Grade 4 either as Thrombosis/embolism (vascular access-related) or Thrombosis/thrombus/embolism in the VASCULAR CATEGORY.						
Pulmonary fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi-basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 – <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 – <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
REMARK: Fibrosis is usually a "late effect" seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic lung tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy. ALSO CONSIDER: Adult Respiratory Distress Syndrome (ARDS); Cough; Dyspnea (shortness of breath); Hypoxia; Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10^9/L) – *Select;* Infection with normal ANC or Grade 1 or 2 neutrophils – *Select;* Infection with unknown ANC – *Select*.						
NAVIGATION NOTE: Recurrent laryngeal nerve dysfunction is graded as Laryngeal nerve dysfunction in the NEUROLOGY CATEGORY.						
Vital capacity	Vital capacity	90 – 75% of predicted value	<75 – 50% of predicted value	<50 – 25% of predicted value	<25% of predicted value	Death
Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	Voice changes	Mild or intermittent hoarseness or voice change, but fully understandable	Moderate or persistent voice changes, may require occasional repetition but understandable on telephone	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; requires voice aid (e.g., electrolarynx) for ≤50% of communication	Disabling; non-understandable voice or aphonic; requires voice aid (e.g., electrolarynx) for >50% of communication or requires >50% written communication	Death
ALSO CONSIDER: Laryngeal nerve dysfunction; Speech impairment (e.g., dysphasia or aphasia).						
Pulmonary/Upper Respiratory – Other (Specify, __)	Pulmonary – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

RENAL/GENITOURINARY						Page 1 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 109/L) – *Select*; Infection with normal ANC or Grade 1 or 2 neutrophils – *Select*; Infection with unknown ANC – *Select*; Pain – *Select*.						
Fistula, GU – *Select*: – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – *Select*	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – *Select* refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

RENAL/GENITOURINARY

Page 2 of 3

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Obstruction, GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – *Select*: – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – *Select*	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – *Select*; Leak (including anastomotic), GU – *Select*; Obstruction, GU – *Select;* Perforation, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

RENAL/GENITOURINARY						Page 3 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Stricture/stenosis (including anastomotic), GU – *Select*: – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – *Select*	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
ALSO CONSIDER: Obstruction, GU – *Select*.						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
ALSO CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*. ALSO CONSIDER: Obstruction, GU – *Select*; Stricture/stenosis (including anastomotic), GU – *Select*.						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

SECONDARY MALIGNANCY

Page 1 of 1

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (Specify, __)	Secondary Malignancy (possibly related to cancer treatment)	—	—	Non-life-threatening basal or squamous cell carcinoma of the skin	Solid tumor, leukemia or lymphoma	Death

REMARK: Secondary malignancy excludes metastasis from initial primary. Any malignancy possibly related to cancer treatment (including AML/MDS) should be reported via the routine reporting mechanisms outlined in each protocol. Important: Secondary Malignancy is an exception to NCI Expedited Adverse Event Reporting Guidelines. Secondary Malignancy is "Grade 4, present" but NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy. A diagnosis of AML/MDS following treatment with an NCI-sponsored investigational agent is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov. Cancers not suspected of being treatment-related are not to be reported here.

SEXUAL/REPRODUCTIVE FUNCTION						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, ≤1/3 of the breast volume; moderate hypoplasia	Asymmetry exists, >1/3 of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – *Select* in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – *Select*.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/ anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	>3 – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for >6 months	—	—

SEXUAL/REPRODUCTIVE FUNCTION						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – *Select*.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

SURGERY/INTRA-OPERATIVE INJURY						Page 1 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Intra-operative hemorrhage is graded as Hemorrhage/bleeding associated with surgery, intra-operative or postoperative in the HEMORRHAGE/BLEEDING CATEGORY.						
Intra-operative injury – *Select Organ or Structure* *'Select'* AEs appear at the end of the CATEGORY.	Intraop injury – *Select*	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: The *'Select'* AEs are defined as significant, unanticipated injuries that are recognized at the time of surgery. These AEs do not refer to additional surgical procedures that must be performed because of a change in the operative plan based on intra-operative findings. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						
Intra-operative Injury – Other (Specify, __)	Intraop Injury – Other (Specify)	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated	Life threatening consequences; disabling	—
REMARK: Intra-operative Injury – Other (Specify, __) is to be used only to report an organ/structure not included in the *'Select'* AEs found at the end of the CATEGORY. Any sequelae resulting from the intra-operative injury that result in an adverse outcome for the patient must also be recorded and graded under the relevant CTCAE Term.						

SURGERY/INTRA-OPERATIVE INJURY – *SELECT*

Page 2 of 2

AUDITORY/EAR
- Inner ear
- Middle ear
- Outer ear NOS
- Outer ear-Pinna

CARDIOVASCULAR
- Artery-aorta
- Artery-carotid
- Artery-cerebral
- Artery-extremity (lower)
- Artery-extremity (upper)
- Artery-hepatic
- Artery-major visceral artery
- Artery-pulmonary
- Artery NOS
- Heart
- Spleen
- Vein-extremity (lower)
- Vein-extremity (upper)
- Vein-hepatic
- Vein-inferior vena cava
- Vein-jugular
- Vein-major visceral vein
- Vein-portal vein
- Vein-pulmonary
- Vein-superior vena cava
- Vein NOS

DERMATOLOGY/SKIN
- Breast
- Nails
- Skin

ENDOCRINE
- Adrenal gland
- Parathyroid
- Pituitary

ENDOCRINE (*continued*)
- Thyroid

HEAD AND NECK
- Gingiva
- Larynx
- Lip/perioral area
- Face NOS
- Nasal cavity
- Nasopharynx
- Neck NOS
- Nose
- Oral cavity NOS
- Parotid gland
- Pharynx
- Salivary duct
- Salivary gland
- Sinus
- Teeth
- Tongue
- Upper aerodigestive NOS

GASTROINTESTINAL
- Abdomen NOS
- Anal sphincter
- Anus
- Appendix
- Cecum
- Colon
- Duodenum
- Esophagus
- Ileum
- Jejunum
- Oral
- Peritoneal cavity
- Rectum
- Small bowel NOS

GASTROINTESTINAL (*continued*)
- Stoma (GI)
- Stomach

HEPATOBILIARY/ PANCREAS
- Biliary tree-common bile duct
- Biliary tree-common hepatic duct
- Biliary tree-left hepatic duct
- Biliary tree-right hepatic duct
- Biliary tree NOS
- Gallbladder
- Liver
- Pancreas
- Pancreatic duct

MUSCULOSKELETAL
- Bone
- Cartilage
- Extremity-lower
- Extremity-upper
- Joint
- Ligament
- Muscle
- Soft tissue NOS
- Tendon

NEUROLOGY
- Brain
- Meninges
- Spinal cord

NERVES:
- Brachial plexus
- CN I (olfactory)
- CN II (optic)
- CN III (oculomotor)
- CN IV (trochlear)

NEUROLOGY (*continued*)

NERVES:
- CN V (trigeminal) motor
- CN V (trigeminal) sensory
- CN VI (abducens)
- CN VII (facial) motor-face
- CN VII (facial) sensory-taste
- CN VIII (vestibulocochlear)
- CN IX (glossopharyngeal) motor pharynx
- CN IX (glossopharyngeal) sensory ear-pharynx-tongue
- CN X (vagus)
- CN XI (spinal accessory)
- CN XII (hypoglossal)
- Cranial nerve or branch NOS
- Lingual
- Lung thoracic
- Peripheral motor NOS
- Peripheral sensory NOS
- Recurrent laryngeal
- Sacral plexus
- Sciatic
- Thoracodorsal

OCULAR
- Conjunctiva
- Cornea
- Eye NOS
- Lens
- Retina

PULMONARY/UPPER RESPIRATORY
- Bronchus
- Lung
- Mediastinum
- Pleura
- Thoracic duct
- Trachea
- Upper airway NOS

RENAL/GENITOURINARY
- Bladder
- Cervix
- Fallopian tube
- Kidney
- Ovary
- Pelvis NOS
- Penis
- Prostate
- Scrotum
- Testis
- Ureter
- Urethra
- Urinary conduit
- Urinary tract NOS
- Uterus
- Vagina
- Vulva

SYNDROMES

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
NAVIGATION NOTE: Acute vascular leak syndrome is graded in the VASCULAR CATEGORY.						
NAVIGATION NOTE: Adrenal insufficiency is graded in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Adult Respiratory Distress Syndrome (ARDS) is graded in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Alcohol intolerance syndrome (antabuse-like syndrome)	Alcohol intolerance syndrome	—	—	Present	—	Death
REMARK: An antabuse-like syndrome occurs with some new anti-androgens (e.g., nilutamide) when patient also consumes alcohol.						
NAVIGATION NOTE: Autoimmune reaction is graded as Autoimmune reaction/hypersensitivity (including drug fever) in the ALLERGY/IMMUNOLOGY CATEGORY.						
Cytokine release syndrome/acute infusion reaction	Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; pressor or ventilatory support indicated	Death
REMARK: Cytokine release syndromes/acute infusion reactions are different from Allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hrs of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Bronchospasm, wheezing; Dyspnea (shortness of breath); Hypertension; Hypotension; Hypoxia; Prolonged QTc interval; Supraventricular and nodal arrhythmia – *Select*; Ventricular arrhythmia – *Select*.						
NAVIGATION NOTE: Disseminated intravascular coagulation (DIC) is graded in the COAGULATION CATEGORY.						
NAVIGATION NOTE: Fanconi's syndrome is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						
Flu-like syndrome	Flu-like syndrome	Symptoms present but not interfering with function	Moderate or causing difficulty performing some ADL	Severe symptoms interfering with ADL	Disabling	Death
REMARK: Flu-like syndrome represents a constellation of symptoms which may include cough with catarrhal symptoms, fever, headache, malaise, myalgia, prostration, and is to be used when the symptoms occur in a cluster consistent with one single pathophysiological process.						
NAVIGATION NOTE: Renal tubular acidosis is graded as Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) in the RENAL/GENITOURINARY CATEGORY.						

SYNDROMES						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
"Retinoic acid syndrome"	"Retinoic acid syndrome"	Fluid retention; less than 3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Mild to moderate signs/ symptoms; steroids indicated	Severe signs/symptoms; hospitalization indicated	Life-threatening; ventilatory support indicated	Death
REMARK: Patients with acute promyelocytic leukemia may experience a syndrome similar to "retinoic acid syndrome" in association with other agents such as arsenic trioxide. The syndrome is usually manifested by otherwise unexplained fever, weight gain, respiratory distress, pulmonary infiltrates and/or pleural effusion, with or without leukocytosis. ALSO CONSIDER: Acute vascular leak syndrome; Pleural effusion (non-malignant); Pneumonitis/pulmonary infiltrates.						
NAVIGATION NOTE: SIADH is graded as Neuroendocrine: ADH secretion abnormality (e.g., SIADH or low ADH) in the ENDOCRINE CATEGORY.						
NAVIGATION NOTE: Stevens-Johnson syndrome is graded as Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) in the DERMATOLOGY/SKIN CATEGORY.						
NAVIGATION NOTE: Thrombotic microangiopathy is graded as Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) in the COAGULATION CATEGORY.						
Tumor flare	Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death
REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. ALSO CONSIDER: Calcium, serum-high (hypercalcemia).						
Tumor lysis syndrome	Tumor lysis syndrome	—	—	Present	—	Death
ALSO CONSIDER: Creatinine; Potassium, serum-high (hyperkalemia).						
Syndromes – Other (Specify, __)	Syndromes – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

VASCULAR

Page 1 of 2

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	Acute vascular leak syndrome	—	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	Peripheral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (≥24 hrs) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end organ damage (e.g., limb loss)	Death
Phlebitis (including superficial thrombosis)	Phlebitis	—	Present	—	—	—
ALSO CONSIDER: Injection site reaction/extravasation changes.						
Portal vein flow	Portal flow	—	Decreased portal vein flow	Reversal/retrograde portal vein flow	—	—
Thrombosis/embolism (vascular access-related)	Thrombosis/embolism (vascular access)	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Thrombosis/thrombus/ embolism	Thrombosis/thrombus/ embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Vessel injury-artery – *Select*: – Aorta – Carotid – Extremity-lower – Extremity-upper – Other NOS – Visceral	Artery injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage (e.g., stroke, MI, organ or limb loss)	Death
NAVIGATION NOTE: Vessel injury to an artery intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						

VASCULAR						Page 2 of 2
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Vessel injury-vein – *Select*: – Extremity-lower – Extremity-upper – IVC – Jugular – Other NOS – SVC – Viscera	Vein injury – *Select*	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); not interfering with ADL; repair or revision not indicated	Symptomatic interfering with ADL; repair or revision indicated	Life-threatening; disabling; evidence of end organ damage	Death
NAVIGATION NOTE: Vessel injury to a vein intra-operatively is graded as Intra-operative injury – *Select Organ or Structure* in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Visceral arterial ischemia (non-myocardial)	Visceral arterial ischemia	—	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (≥24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end organ damage	Death
ALSO CONSIDER: CNS cerebrovascular ischemia.						
Vascular – Other (Specify, __)	Vascular – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death