STATISTICAL ANALYSIS PLAN

Title:	A Long-Term Follow-up Study to Evaluate the Safety and Efficacy of Adeno Associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Glucose-6-Phosphatase (G6Pase) in Adults with Glycogen Storage Disease Type Ia (GSDIa)
Protocol:	401GSDIA02
Investigational Product:	DTX401
Phase:	1/2
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV8	adeno-associated virus serotype 8
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASR	antigen specific response
BMI	body mass index
CFC	controlled fasting challenge
CGM	continuous glucose monitoring
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot assay
G6Pase	glucose-6-phosphatase
GSDIa	glycogen storage disease type Ia
IgG	immunoglobulin G
IP	investigational product
IRR	infusion-related reaction
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PDFF	proton density fat fraction
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PROMIS	Patient reported outcomes measurement information system
PSQI	Pittsburgh Sleep Quality Index
PT	preferred term
HRQoL	health-related quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event

DOCUMENT REVISION HISTORY

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Study 401GSDIA02 is a long-term follow-up study to evaluate the safety and efficacy of adeno-associated virus serotype 8 (AAV8)-mediated gene transfer of glucose-6-phosphatase (G6Pase) in adults with glycogen storage disease type Ia (GSDIa). Only subjects who received DTX401 in Study 401GSDIA01 are eligible to participate in Study 401GSDIA02. Study 401GSDIA01 was a Phase 1/2, open-label safety and dose-finding study of AAV8-mediated gene transfer of G6Pase in adults with GSDIa, during which subjects received a single intravenous (IV) dose of DTX401. No investigational product will be administered during Study 401GSDIA02.

1.2. Objectives of Analysis

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the 401GSDIA02 Protocol Amendment 4 dated 3 April 2023.

2. STUDY OBJECTIVE(S)

2.1. Primary Objective(s) and Endpoint(s)

The primary objective of the study is as follows:

- To determine the long-term safety of DTX401 following a single IV dose in adults with GSDIa

The primary endpoint of this study is as follows:

- The incidence of AEs and SAEs for each cohort and overall assessed by severity and relationship to IP

2.2. Secondary Objective(s) and Endpoint(s)

The secondary objective of the study is as follows:

- To evaluate the long-term effect of DTX401 on symptom-free euglycemia in a setting of a controlled fasting challenge

The secondary endpoint of this study is as follows:

- The change from Day 0 (Study 401GSDIA01) in time to first hypoglycemic event during a controlled fasting challenge over time by cohort and overall, following IV administration of DTX401

2.3. Tertiary Objectives and Endpoints (s)

The tertiary objectives of this study are as follows:

- To evaluate the long-term effect of DTX401 on lipid profiles (total cholesterol, low-density lipoprotein, and triglycerides)
- To evaluate the long-term effect of DTX401 on uric acid
- To evaluate the long-term effect of DTX401 on proteinuria
- To evaluate the long-term effect of DTX401 on liver size and fat content
- To evaluate the long-term effect of DTX401 on hepatic adenoma progression
- To assess the long-term impact of DTX401 on cornstarch requirements
- To assess the long-term impact of DTX401 on glucose homeostasis
- To assess the long-term impact of DTX401 on the subject's health-related quality of life (HRQoL) and sleep quality
- To describe the long-term immune response to AAV8 capsid proteins after IV administration of DTX401
- To describe the long-term immune response to G6Pase after IV administration of DTX401
- To evaluate the long-term effect of DTX401 on lactate levels

- To evaluate the long-term effects of DTX401 on the endocrine and metabolic responses to fasting

The tertiary endpoints of this study are as follows:

- Total cholesterol, low-density lipoprotein, and triglycerides, by time point, cohort, and overall
- Uric acid, by time point, cohort, and overall
- 24-hour urine protein, by time point, cohort, and overall
- The change from baseline in liver size and fat fraction (by MRI) over time following IV administration of DTX401, by cohort, and overall
- The average daily use of cornstarch (or equivalent) over time, by cohort, and overall
- Assessment of serum glucose levels over time, summarized by cohort
- Subject responses to HRQoL and sleep quality assessments over time following IV administration of DTX401, by cohort and overall
- Year 2 – Exit Interviews
- The development of neutralizing antibodies to AAV8 (as determined by a cell-based assay) over time, by cohort, and overall
- The development of anti-AAV8 binding antibodies (as determined by ELISA) over time, by cohort, and overall
- The development of anti-G6Pase antibodies over time, by cohort, and overall
- Assessment of lactate levels over time, summarized by cohort and overall

2.4. Estimands

Not applicable.

3. STUDY DESIGN

In Study 401GSDIA01, subjects were followed for 1 year after dosing with DTX401. In Study 401GSDIA02, subjects will be followed for at least 3 additional years (and up to 5 additional years) for a total of 4-6 years of follow-up after administration of DTX401.

The first visit for Study 401GSDIA02 (Visit 1) may coincide with the Week 52/EOS/EW visit for Study 401GSDIA01. Subjects will visit the study site approximately every 13 weeks during the first year of Study 401GSDIA02 and then approximately every 26 weeks through the end of the study at Week 312 (Year 6) for safety and efficacy evaluations.

A long-term disease monitoring program (DMP) DTX401-CL401 is planned. Once the DMP is available to enroll, and after subjects reach the Week 208 visit (Year 4) in Study 401GSDIA02, subjects will transition to the DMP with Sponsor approval.

3.1. Study Population

Subjects dosed with DTX401 in Study 401GSDIA01 and who have met eligibility criteria for Study 401GSDIA02 study will be enrolled in Study 401GSDIA02.

3.2. Dosage and Administration

No investigational product will be administered during Study 401GSDIA02. All subjects enrolled in Study 401GSDIA02 will have received a single IV dose of DTX401 during their participation in Study 401GSDIA01.

3.3. Blinding and Randomization Methods

Not applicable.

3.4. Potential Covariate(s)

Not applicable.

3.5. Subgroups

Not applicable.

3.6. Sample Size Considerations

The study is expected to enroll up to 12 subjects. The sample size is not based on a power calculation.

3.7. Statistical Hypothesis

No formal statistical hypothesis testing will be performed.

3.8. Multiple Comparisons/Multiplicity

Not applicable.

3.9. Interim Analysis

Administrative analyses may be performed during the study to support registrational activities or respond to regulatory inquiries.

3.10. Data Monitoring Committee

Not Applicable.

4. DEFINITIONS

4.1. Baseline

Baseline is defined as the last non-missing assessment taken prior to the dose of DTX401 in Study 401GSDIA01, unless specified otherwise.

4.2. Study Day

If the visit date is on or after the date of the dose of DTX401:

Study day = (visit date – date of the dose of DTX401 + 1)

If the visit date is prior the date of the dose of DTX401:

Study day = visit date – date of the dose of DTX401.

4.3. Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al., 2013), (NIH, 2015). It uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. High scores indicate more of the concept being measured. The domain-specific approach is based on the idea that health attributes, such as pain and physical function are not unique to a specific disease. The PROMIS contains a bank of questions from which relevant items can be extracted and used to create a custom form.

The PROMIS-29 profile (v2.1) (Appendix 3) is a profile measure designed for adults that includes a collection of seven 4-item short forms assessing domain scores for anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, and ability to participate in social roles and activities as well as a single pain intensity item. The single pain intensity item is not scored but reported as its raw score (e.g., 0 to 10).

Each domain has one or more items, and each item has five response options ranging in value from 1 to 5. The score interpretation is included in Table 1.

Table 1: Numerical Scoring of Adult Domains

	Worst Score	Best Score
Physical Function/Ability to Participate in Social Roles and Activities	1	5
Fatigue/Sleep Disturbance/Pain Interference /Cognitive Function/Anxiety/Depression	5	1

The raw score for a domain can be derived as follows:

$$\frac{\text{Raw sum} \times \text{number of items on the domain}}{\text{Number of items that were actually answered on the domain}}$$

The PROMIS Social Isolation (Appendix 4) is a 4-item short form assessing perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others.

4.4. Pittsburgh Sleep Quality Index

CCI

[redacted]

4.5. Patient Global Impression of Severity (PGI-S) And Patient Global Impression of Change (PGI-C)

The 5-point PGI-S instrument will be administered to ascertain patient perception of disease severity (Appendix 6). The PGI-C is a self-completed measure to assess the patient's view of improvement from baseline and is rated on a 7-point categorical scale ranging from 'much improved' to 'much worse' (Appendix 7)

5. ANALYSIS SETS

5.1. Full Analysis Set (FAS)

The full analysis set will consist of all subjects enrolled in Study 401GSDIA02 and have received a dose of DTX401 in Study 401GSDIA01. Unless specified otherwise, the full analysis set will be used for all the analyses.

6. STATISTICAL ANALYSIS

6.1. General Principles

All analyses in the study will be descriptive; no formal hypotheses will be tested. An integrated analysis using data from both Study 401GSDIA01 and Study 401GSDIA02 will be performed to summarize and assess the long-term safety and efficacy of DTX401; there will not be a standalone analysis of data from only Study 401GSDIA02.

Continuous variables will be summarized by number of subjects, mean, SD, standard error (SE), median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. All summary tables will be presented by scheduled study visit and no analysis windows will be used, unless specified otherwise. Study visits from both studies 401GSDIA01 and 401GSDIA02 will be included in summary tables.

All summary tables will be presented by dose cohort of DTX401 (see below), Cohorts 2, 3, 4 combined (i.e., cohorts for dose 2 combined), and overall, unless specified otherwise.

The dosing cohorts are:

- Cohort 1: Dose 1 (2.0×10^{12} GC/kg) with a reactive steroid regimen (prednisone starting dose of 40 mg/day)
- Cohort 2: Dose 2 (6.0×10^{12} GC/kg) with a reactive steroid regimen (prednisone starting dose of 40 mg/day)
- Cohort 3: Dose 2 (6.0×10^{12} GC/kg) with an optimized reactive steroid regimen (prednisone starting dose of 60 mg/day)
- Cohort 4: Dose 2 (6.0×10^{12} GC/kg) with a prophylactic steroid regimen

SAS® software version 9.4 or higher will be used to perform statistical analyses unless otherwise specified.

Handling of missing or incomplete data is described in Appendix 1.

6.2. Subject Accountability

The number and percentage of subjects who complete Study 401GSDIA02 and of subjects who prematurely discontinue Study 401GSDIA02 will be summarized. The reasons for premature discontinuation from the study will be summarized as recorded in the electronic case report forms (eCRFs). The study duration will be summarized. The study duration is defined as date of Study 401GSDIA02 completion/discontinuation – DTX401 dose date +1. Number of subjects completing 1, 2, 3, 4, 5, and 6 years of study will be provided. A subject disposition listing, including study duration, will be provided.

For subjects who fail to meet eligibility criteria for Study 401GSDIA02, the inclusion/exclusion criteria the subjects fail will be listed.

6.3. Protocol Deviations

Major protocol deviations in Study 401GSDIA02 will be summarized for each type. Both major and minor protocol deviations will be listed.

6.4. Investigational Product Administration

Not applicable because no investigational product (IP) will be administered during Study 401GSDIA02.

6.5. Demographic and Baseline Characteristics

Demographic and baseline data captured in Study 401GSDIA01 is summarized and listed as part of the clinical study report for that study; demographic information captured in Study 401GSDIA02 at the study entry will not be summarized or listed separately.

6.6. General Medical History

Medical history of subjects prior to dosing captured in Study 401GSDIA01 is summarized and listed as part of the clinical study report for that study. Medical history prior to study entry will also be collected at Visit 1 in Study 401GSDIA02 and will mainly include any AEs that are ongoing at the completion of Study 401GSDIA01. This data will be listed by subject.

6.7. Prior and Concomitant Medication

Prior medications are defined as medications that started before the dosing and they are summarized and listed as part of Study 401GSDIA01 Clinical Study Report. Concomitant medications are defined as any medications taken on or after the dosing date. Concomitant medications from Study 401GSDIA01 are summarized and listed as part of its clinical study report. Concomitant medications data captured in Study 401GSDIA02 will be summarized separately. Further, concomitant medications data from both studies 401GSDIA01 and 401GSDIA02 will be combined and summarized and listed as well. Concomitant medications will be coded by drug name and therapeutic class using WHO Drug dictionary. If a subject received a specific medication multiple times or received multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

6.8. Efficacy Analysis

The efficacy analyses will be based on the Full Analysis Set.

6.8.1. Symptom-Free Euglycemia (Controlled Fasting Challenge)

Subject's ability to maintain symptom-free euglycemia during controlled fasting challenge (CFC) will be measured by the time to first hypoglycemic event during CFC or equivalently the duration of CFC. Duration of CFC is defined as time (in hours) from start of CFC to the end of CFC (as documented on eCRF). CFC ends when any of the following 3 conditions are met: 1) glucose <54 mg/dL; 2) signs/symptoms of hypoglycemia; or 3) 15 hours fasting without hypoglycemia. Change from baseline will be calculated using results on Day 0 in Study 401GSDIA01 as baseline.

Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis. Duration of CFC and change from baseline will be summarized by visit. Use of cornstarch and carbohydrates in the dinner prior to controlled fasting challenge and change from baseline will be summarized by visit. A listing of CFC data will be provided.

Since subjects can receive different amounts of carbohydrates in their dinner and cornstarch prior to the CFC due to individualized prescription for their meals and cornstarch, a summary of duration of CFC normalized by amount of cornstarch consumed before the CFC and change from baseline will be provided. Normalized CFC duration will be calculated as CFC duration divided by the pre-CFC cornstarch (grams) and it will denote the gain in CFC duration (in minutes) per gram of cornstarch. Similarly, a summary of duration of CFC normalized by amount of carbohydrates consumed before the CFC and change from baseline will be provided. Normalized CFC duration will be calculated as CFC duration divided by the sum of carbohydrates in the dinner and cornstarch prior to the CFC and it will denote the gain in CFC duration (in minutes) per gram of carbohydrates.

Plots for individual patient profile of CFC duration and change from baseline in CFC duration by visit will be provided. Additional plots will include CFC duration (and change from baseline) and indicators for inappropriately high insulin level or inappropriately low cortisol levels during the CFC if that data is collected during the CFC. Insulin response is deemed inappropriate if ≥ 25 µIU/mL at the start of the challenge or > 2µIU/L at the end of the challenge. Cortisol response is deemed inappropriate if < 10 µg/dL at the end of the challenge. Plots will also be provided for normalized CFC duration (by the amount of pre-CFC cornstarch).

Pre-CFC whole blood lactate and rate of rise of lactate during the CFC (calculated as the slope between the lactate value at the start of CFC and peak lactate value during the CFC, expressed as mmol/L/h) and change from baseline will be summarized by visit. Pre-CFC analyte value is the value collected nearest to the start time of the CFC and within +/- 30 minutes of start time of CFC. End-CFC analyte value is the value collected nearest to the end time of the CFC and within +/- 30 minutes of end time of CFC. Peak analyte value during the CFC is the maximum analyte value observed any time from the start time of CFC to the end time of the CFC and including pre-CFC and end-CFC analyte values.

Similarly, pre-CFC plasma glucose and rate of decline of glucose during the CFC and change from baseline will be summarized by visit. Trough analyte value during the CFC is the minimum analyte value observed any time from the start time of CFC to the end time of the CFC, including pre-CFC and end-CFC values (defined above). Rate of decline of glucose will be calculated as the slope between the pre-CFC glucose value and trough glucose value during the CFC, expressed as mg/dL/h.

In addition, plots for individual patient profile of glucose and lactate levels during CFC will be presented by study visits. Plot for individual patient profile of glucose and ketones levels during CFC will be presented by study visit where that data was collected.

A listing of metabolic lab parameters (glucose, lactate, ketones, free fatty acids, alanine), and hormonal lab parameters (cortisol, ACTH, glucagon, insulin, C-peptide, growth hormone, IGFBP1) collected before and during the controlled fasting challenges will be provided.

6.8.2. Use of Cornstarch (or Glycosade)

Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis. The prescribed and actual daily amount (g) and frequency of cornstarch over time, change from baseline and percent change from baseline will be summarized by study visit and provided in the listings. Summary will also be provided for daily cornstarch intake (g) per kg of body weight

over time. Summary may be provided at last available study visit for a subject if deemed appropriate. In addition, the percent change from baseline in prescribed and actual daily cornstarch amount by study visit will be plotted for each subject. Further, daytime cornstarch intake and nighttime cornstarch intake will be summarized. Daytime cornstarch frequency and nighttime cornstarch frequency will be summarized.

Prescribed and actual daily frequency of cornstarch by study visit will be plotted for each subject along with information on daily amount of cornstarch. Daily daytime and nighttime frequency of cornstarch (prescribed and actual) will be plotted by visit for each subject.

Further, average duration of dosing interval and change from baseline will be analyzed separately for daytime and nighttime doses. For each dose, duration of dosing interval is calculated as the time (in hours) from current dose to the next dose.

Data collected at a scheduled visit within an analysis window of +/- 14 days of the target day for a visit up to Week 52, within an analysis window of +/- 21 days of the target day for visits post Week 52 and up to Week 104 and within an analysis window of +/- 42 days of the target day for visits post Week 104 will be included in the analysis. If such a scheduled visit is not performed, data collected at the nearest unscheduled visit (if any) completed within that analysis window will be included.

6.8.3. GSDIa Diet (Non-Cornstarch)

Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis. The prescribed and actual daily GSDIa non-cornstarch diet parameters and change from baseline values will be summarized by study visit. Diet parameters will include total calories, amounts of individual macronutrients (carbohydrates, non-utilizable sugars, protein, and fat), % of total calories from individual macronutrients, and non-utilizable sugars as % of total carbohydrates. Total calories in diet will be derived from individual macronutrients as follows:

Total calories (Kcal)= 4 x amount of carbohydrates (g)+ 9 x amount of fat(g) + 4 x amount of protein (g).

Summary may be provided at last study visit if deemed appropriate. Individual subject listing of GSDIa diet data will be provided.

Data collected at a scheduled visit within an analysis window of +/- 14 days of the target day for a visit up to Week 52 and within an analysis window of +/- 21 days of the target day for visits post Week 52 and up to Week 104 and within an analysis window of +/- 42 days of the target day for visits post Week 104 will be included in the analysis. If such a scheduled visit is not performed, data collected at the nearest unscheduled visit (if any) completed within that analysis window will be included.

Further, total calories from diet and cornstarch and % of total calories (cornstarch and diet combined) from individual macronutrients will be summarized by study visit. Total calories (Kcal) from cornstarch will be derived as 3.75 x amount of cornstarch (g).

Plot of mean % of total calories from individual macronutrients by study visit will be provided.

6.8.4. Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) device data was collected for only cohort 3 and 4 in Study 401GSDIA01. It will be collected for all subjects in Study 401GSDIA02. Available data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis. CGM values less than 40 mg/dL or greater than 400 mg/dL will not be included in the analysis because they are not considered as reliable values being outside the Dexcom G6 reportable range of 40-400 mg/dL.

Percentage of glucose values in different glucose ranges (<54, <60, <70, 60-120, 70-120, >120 mg/dL) together with cornstarch intake (in grams) will be plotted by visit for each subject along with the actual cornstarch use at the visit. CGM data in 4 weeks prior to the visit will be used to calculate the percentage of glucose values in any range. Percentage of glucose values in any glucose range for a visit is calculated as number of glucose values in that range in a 4-week period prior to the visit, divided by total number of glucose values in that 4-week period and multiplied by 100. Further, mean percentage of glucose values in different glucose ranges (<54, <60, <70, 60-120, 70-120, >120 mg/dL) together with mean actual cornstarch intake (in grams) will be plotted by visit for each cohort.

Time spent below 70 mg/dL in 4 weeks prior to the visit will be plotted by visit for each subject. Time duration (in minutes) of glucose values spent in a range is calculated as sum of all the time intervals where glucose value is in that range. Time interval for any glucose value is calculated as the difference between collection time of that glucose value and the next collection time. Glucose values are usually collected approximately every 5 minutes, however if the glucose value is missing at any collection time the last available glucose value prior to the collection time will be carried forward if that value is collected within 15 minutes.

Number and total duration of hypoglycemic events in 4 weeks prior to the visit will be plotted by visit for each subject together with actual cornstarch use at a visit. A hypoglycemic event is defined as a series of at least two sensor glucose values less than 54 mg/dL that are at least 15 minutes apart with no intervening values of 54 mg/dL or more. The end of a hypoglycemic event is defined as at least two sensor glucose values > 70 mg/dL that are at least 15 minutes apart with no intervening values <70 mg/dL. Similar plots will be provided for nocturnal hypoglycemic events. Summary of number and duration of hypoglycemic events in 4 weeks prior to the visit will be provided.

6.8.5. Morning Glucose Levels

If a subject is unable to use the assigned CGM, the subject should collect morning glucose levels at least 2 mornings per week throughout the study. Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

Individual morning glucose levels will be summarized by visit and provided in the listings. Data collected in 4 weeks prior to the visit will be included in the analysis. Plots for individual patient profile of weekly mean morning glucose level and overnight cornstarch dose (as reported in morning glucose level eCRF) will also be presented.

6.8.6. Liver Magnetic Resonance Imaging and Ultrasound

Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

Descriptive statistics for liver MRI results, including mean proton density fat fraction (PDFF) across liver segments (%) and liver volume (ml), and change from Study 401GSDIA01 baseline values will be summarized by study visit. Each MRI will be interpreted as "normal", "abnormal not clinically significant", or "abnormal clinically significant". The interpretation of the MRI data will be summarized by study visit using a shift table. A listing of all MRI results including the interpretation will be provided.

Descriptive statistics for liver ultrasound results (interpreted as "normal", "abnormal not clinically significant", or "abnormal clinically significant") will be summarized by study visit. A listing of liver ultrasound results will be provided.

6.8.7. Health-Related Quality of Life and Sleep Quality

The observed values over time and change from Study 401GSDIA01 baseline values will be summarized for quality-of-life related measures. Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

Listings for the HRQoL (PROMIS-29, PROMIS Social Isolation, PGI-S, and PGI-C) and sleep quality (PSQI) assessments will be provided. Summary of percent change from baseline in actual cornstarch intake by PGIC will be provided by visit.

Findings from endpoint outcomes interview (Year 2 - exit interview) will be described in a qualitative manner.

6.9. Safety Analysis

The safety analysis will be performed using the FAS. The safety parameters will include AEs, SAEs, vital sign measurements, physical examination findings, electrocardiogram (ECG) results, subject reported symptomatic hypoglycemic events, clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, coagulation panel, and urinalysis), vector shedding, vector genome determination, measurement of neutralizing antibody titer to AAV8, measurement of AAV8 binding antibody immunoglobulin G (IgG), assessment of any cell-mediated immune responses to AAV8 and G6Pase, and measurement of anti-G6Pase antibodies.

6.9.1. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the current version of Medical Dictionary for Regulatory Activities.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose of IP.

AEs from both studies 401GSDIA01 and 401GSDIA02 will be combined for this analysis. Further, AEs from Study 401GSDIA02 will also be summarized separately.

Subject incidence of TEAEs will be tabulated as the follows. The number of events will also be included.:

- Summary of TEAEs
- TEAEs by SOC and PT
- Related TEAEs by SOC and PT

- Serious Related TEAEs by SOC and PT
- Grade 3 or 4 TEAEs by SOC and PT
- Fatal TEAEs by SOC and PT
- TEAEs leading to discontinuation of study by SOC and PT
- TEAEs by PT
- TEAEs by PT and greatest severity
- TEAEs by their time of occurrence (<1, 1-2, 2-3, 3-4, 4-5, 5-6 years since the IP administration)

The severity will be based on the most current version of CTCAE. If an AE cannot be graded based on CTCAE, the investigator will assign a severity based on 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death. Detailed listings for all AEs, serious TEAEs, TEAEs leading to the discontinuation of study, and death will also be generated.

6.9.1.1. Important Potential Risks and Adverse Events of Special Interest (AESI)

Vector-induced hepatic effects (e.g., increased aminotransferase levels) following IP administration and infusion-related reactions (IRR) including hypersensitivity during or following IP administration have been identified as important potential risks and adverse events of special interest (AESIs) for DTX401. Since subjects are enrolled in Study 401GSDIA02 at 52 weeks after IP infusion in Study 401GSDIA01, it is not expected that any IRRs will be observed in Study 401GSDIA02 and will be considered as not applicable for this study.

MedDRA search strategy to identify PTs for vector-induced hepatic effects is included in Appendix 2. Subject Incidence of TEAEs of vector-induced hepatic effects will be tabulated by SOC and PT.

6.9.1.2. Potential Risks and Adverse Events of Special Interest

Adrenal insufficiency is considered a potential risk of study-related procedures associated with use of corticosteroids and is an AESI. Since subjects are enrolled in Study 401GSDIA02 at 52 weeks after IP infusion in Study 401GSDIA01, it is not expected that corticosteroids will be administered in 401GSDIA02 study to minimize or prevent potential vector-inducted hepatic events (eg, transaminase elevations). However, in the event elevated ALT or AST is observed in 401GSDIA02 study due to the AAV8 vector and corticosteroids are required (and is not due to underlying disease), subject incidence of TEAEs of adrenal insufficiency will be tabulated by SOC and PT. MedDRA search strategy to identify PTs for these events is included in Appendix 2.

6.9.1.3. Potential Risk

Dorsal Root Ganglion and Peripheral Nerve Effect following IP administration has been identified as a potential risk for DTX401. MedDRA search strategy to identify PTs for these events is included in Appendix 2. Subject Incidence of TEAEs of potential risk will be tabulated by SOC and PT.

6.9.1.4. AAV Gene Therapy Class Effects

AAV gene therapy class effects include malignancies (new or worsening of pre-existing malignancies) and thrombotic microangiopathy. The MedDRA search strategies to identify PTs for these events is included in Appendix 2. Subject Incidence of TEAEs for AAV gene therapy class effects will be tabulated by SOC and PT.

6.9.2. Physical Examination

Physical examination findings in Study 401GSDIA02 will be listed by study visit. Physical examination findings that are clinically significant per study investigator are documented and summarized as AEs.

6.9.3. Clinical Laboratory Assessments

Clinical laboratory assessments are mainly collected at central laboratory, except for data collected during CFC which is collected at local laboratory and analyzed as described in Section 6.8.1. In some cases, subjects may complete safety labs (i.e., chemistry, hematology, etc.) at a local laboratory instead of at scheduled visit at a site or a home healthcare visit. That data will be mapped to appropriate scheduled visits if they are collected within +/- 14 days window from the scheduled visit date.

For all central clinical laboratory parameters (Table 2) with continuous results, absolute values and changes from baseline will be summarized by study visit. For central laboratory parameters with categorical results, results will be included in a listing because these parameters are non-critical for analysis (e.g., Urinalysis blood (by dipstick), or microscopic examination parameters, etc.). Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

Quantitative laboratory measurements reported as "< X", i.e., below the lower limit of quantification will be converted to X/2 for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" in the listings. Quantitative laboratory measurements reported as "> X", i.e., above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "> X" in the listings. In the event of repeat laboratory assessments, the last non missing value will be used.

Severity of selected chemistry and hematology laboratory parameters will be graded according to the version 5.0 of CTCAE (Appendix 8) where severity grading criteria are available. Shift tables using CTCAE grades to compare baseline to the worst post-baseline value will be produced for hematology and chemistry laboratory parameters. For some specific parameters with CTCAE grading in both high and low direction (e.g., glucose, potassium, sodium), CTCAE grades in high and low directions will be presented separately, i.e., hyper for higher values of concern and hypo for lower values of concern. Values from post-baseline unscheduled visits will also be considered when the worst post-baseline value is derived.

Listings of laboratory parameters will be provided. Individual patient profile of triglyceride with daily cornstarch intake over time will be plotted. Individual patient profile of ALT, AST, and prednisone/prednisolone dose over time will be plotted. Listings of selected laboratory parameters will be provided for subjects satisfying Hy's law criteria (if any). Any abnormal laboratory test results which are considered as clinically significant in the medical and scientific judgment of the Investigator, are to be recorded as AEs or SAEs.

Table 2: Central Clinical Laboratory Parameters

Clinical chemistry	Lipid panel, uric acid, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, albumin, total protein, creatine kinase, bilirubin (total, direct, and indirect), ALT, AST, ALP, gamma-glutamyl transferase, and lactate dehydrogenase
Hematology	Complete blood count with differential
Urinalysis	Specific gravity, pH, glucose, protein, blood (by dipstick), ketones (by dipstick), and microscopic examination (if blood or protein is found)
Coagulation panel	PT/INR, aPTT
24-Hour urine	Total protein, microalbumin, and creatinine

Abbreviations ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; PT/INR = prothrombin time/international normalized ratio.

6.9.4. Vital Signs

Vital sign measurements (heart rate in beats per minute, blood pressure [seated systolic and diastolic] in millimeters of mercury (mm Hg), and respiratory rate in millimeters of mercury (mm Hg)), and changes from baseline values will be summarized by study visit. Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

Vital sign values will be considered clinically significant if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 3. The number and percentage of subjects with clinically significant post-baseline values will be tabulated. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator will be the total number of subjects with available baseline values and at least 1 clinically significant post-baseline value.

Table 3: Criteria for Clinically Significant Vital Signs

Parameter	**Flag**	**Criteria**	
		Observed Value	**Change from Baseline**
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 60	Decrease of ≥ 15

Weight, and BMI will be summarized by visit. Summary may be provided at last study visit as if deemed appropriate. BMI at a visit will be calculated using weight at that visit and height at screening visit in Study 401GSDIA01. Individual subject listing of vital signs will be provided. If a clinically significant change or abnormal vital sign measurement is observed per study investigator, it should be recorded as an AE or SAE.

6.9.5. Electrocardiogram

A listing of ECG results at Visit 1 (Week 52) in Study 401GSDIA02 will be provided. A single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT intervals.

6.9.6. Symptomatic Hypoglycemic Events

The number of subjects reporting symptomatic hypoglycemic events as captured in eCRF and number of events will be summarized by visit. Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

Details of the symptomatic hypoglycemic events will be provided in a listing.

6.9.7. Immune Response to AAV8 and G6Pase

Neutralizing antibodies to AAV8, AAV8 binding antibody IgG assay, and anti-G6Pase antibody assay will be summarized by study visit. Listings for these safety parameters will be provided. Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

6.9.8. Cell-mediated Immune Response to AAV8 and G6Pase

The presence of T cells specific for AAV8 and G6Pase will be determined by an enzyme-linked immunospot (ELISPOT) assay.

Antigen specific response (ASR) for a subject at a visit will be calculated as M1 – S1 – (M2 + [2xS2]) where M1 and S1 are antigen specific mean spots count and standard deviation and M2 and S2 are medium mean spots count and standard deviation, respectively, at that visit. ASR will be summarized by visit.

ASR will be further categorized as None (ASR $\leq$ 3 or M1 $\leq$ 10), Low (ASR > 3 and $\leq$ 50), Medium (ASR > 50 and $\leq$ 100) or High (ASR > 100) and will be summarized by visit. ASR is not applicable (N/A) if PHA mean spots count is < 100 or Medium mean spots count is greater than 20% of the PHA mean spots count.

Individual subject profiles for ALT and steroid use will be plotted with ASR. Analyses will be repeated by excluding samples with poor PHA response (i.e., lower than expected PHA stimulation response e.g., the result is not “too numerous to count”). Listings of ELISPOT data will be provided. Data from both studies 401GSDIA01 and 401GSDIA02 will be included in this analysis.

6.9.9. Vector Shedding

Blood, saliva, urine, and stool samples for vector shedding were to be collected for subjects who did not demonstrate clearance in Study 401GSDIA01. There was no subject who did not demonstrate clearance in Study 401GSDIA01 study, hence no vector shedding data is expected to be collected in Study 401GSDIA02. A listing of available vector shedding data in Study 401GSDIA02 will be provided if any data is collected.

6.10. Impact of COVID-19 on Study Participation

The study has been ongoing during the COVID-19 pandemic. To capture the impact of COVID-19 on subjects' study participation, the study eCRFs and eCRF completion guidelines were modified during the study as per the regulatory guidance to capture COVID-19 related AEs and reasons for study discontinuation, missed/delayed visits, and missed assessments due to COVID-19 as "COVID-19 related reason". Study data listings will include this information e.g., listing of AEs will include any AEs related to COVID-19 and listing of protocol deviations will include deviations related to missed visits and missed assessments due to COVID-19. These listings will be used to assess any potential impact of COVID-19 on subjects' study participation.

7. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

8. LIST OF PLANNED TABLES AND FIGURES

List of planned tables, figures, and listings will be included in the shell document which will be maintained separately.

9. LITERATURE REFERENCES

Broderick JE, DeWitt EM, Rothrock N, et al. (2013) Advances in Patient-Reported Outcomes: The NIH PROMIS Measures. *EGEMS (Wash DC)* 1(1): 1015.

DHHS (2017) *Common terminology criteria for adverse events (CTCAE) Version 5.0 (27 November 2017)*. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

NIH (2015) *PROMIS*. Available at: http://www.nihpromis.org/default.aspx#6 (accessed January).

10. APPENDICES

APPENDIX 1. HANDLING OF MISSING AND INCOMPLETE DATA

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, only the observed data (not imputed data) will be presented in listings.

Missing Medical History Related Dates

- If only day is missing, impute 1.
- If month is missing, impute January 1st.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is earlier than the birth date, then the birth date will be used.

Missing Birth Dates

To impute missing birth date, the following rules will be applied:

- If day is missing, impute 15.
- If month is missing, impute June.
- If year is missing, then no imputation will be done; the date will be missing.

If the imputed date is later than any study visit date/observed adverse event start date/ observed concomitant medication start date, then earliest available visit date/adverse event start date/ concomitant medication start date will be used without changing observed information.

Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date.

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the month and year of the Visit 1 (Week 52) date, then impute the day of the Visit 1 (Week 52) date.
  - Otherwise, assign the first day of the month.
- If the month is unknown, then:
  - If the year matches the year of the Visit 1 (Week 52) date, then impute the month and day of the Visit 1 (Week 52) date.
  - Otherwise, assign ‘January 1st’

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the imputed date is earlier than birth date, then birth date will be used. If the imputed start date is later than the end date, then the start date will be set as the same date as the end date.

Missing Stop Dates and not ongoing

- If the day is unknown, then assign the last day of the month.
- If the month is unknown, then assign 'December.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing. If the AE has been recorded as resolved/recovered, all efforts should be made to obtain the date from the Investigator.

If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date as close to the date of study completion / discontinuation/ data cutoff as possible without overwritten existing information.

If the year is missing for the start date and stop date (observed or imputed) is on or after the Visit 1 (Week 52) date or event is ongoing, the start date will be imputed as the Visit 1 (Week 52) date.

Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to DTX401 is missing for an AE, a causality of "related" will be assigned. The imputed values for causal relationship to DTX401 will be used for the summary; the values will be shown as missing in the data listings.

APPENDIX 2. MEDDRA SEARCH STRATEGIES FOR AESI AND ADVERSE EVENTS OF POTENTIAL RISK

Following MedDRA search strategy will be used to identify preferred terms for the important potential risk and AESI of Vector-induced hepatic effects:
Drug related hepatic disorders- comprehensive search SMQs (with all 4 sub-SMQs:

- Cholestasis and jaundice of hepatic origin;
- Drug related hepatic disorders – severe events only (includes 4 sub-SMQs);
- Liver related investigations, signs and symptoms;
- Liver related coagulation and bleeding disturbances).

Following MedDRA search strategy will be used to identify preferred terms for the potential risk and AESI of Adrenal insufficiency:

- Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Adrenal suppression, Acute adrenal crisis, Steroid withdrawal syndrome, Glucocorticoid deficiency, Cortisol decreased, Cortisol abnormal, Blood corticotrophin decreased, Blood corticotrophin abnormal, Adrenocorticotropic hormone deficiency, ACTH stimulation test abnormal

Following MedDRA search strategy will be used to identify preferred terms for the potential risk of Dorsal Root Ganglion (DRG) and Peripheral Nerve Effects:

- HLGT Peripheral Neuropathies

Following MedDRA search strategy will be used to identify preferred teams for the AAV gene therapy class effect of malignancies (new or worsening of pre-existing malignancies):

- Malignancies SMQ [(broad + narrow terms) with sub-SMQs of Malignancy related conditions, Malignancy related therapeutic and diagnostic procedures, Malignant or unspecified tumors, Tumor markers]

Following MedDRA search strategy will be used to identify preferred teams for the AAV gene therapy class effect of thrombotic microangiopathy:

- Embolic and Thrombotic Events SMQ [(broad + narrow terms) with sub-SMQs of Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous] and
- Hemolytic disorder SMQ (broad + narrow terms)

APPENDIX 3. PROMIS-29

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
H7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.1

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep120	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.1

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

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APPENDIX 4. PROMIS SOCIAL ISOLATION – SHORT FORM 4A

PROMIS Item Bank v2.0 - Social Isolation – Short Form 4a

Social Isolation –Short Form 4a

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
UCLA11x2	I feel left out.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
UCLA13x3	I feel that people barely know me.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
UCLA14x2	I feel isolated from others	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
UCLA18x2	I feel that people are around me but not with me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

23 June 2016

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CCI

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APPENDIX 6. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Patient Global Impression of Severity (PGIS)

1. Thinking about your GSDIa over the past 7 days, how often did you have low blood sugar?
   - ☐ Never
   - ☐ 1 or 2 times
   - ☐ 3 to 5 times
   - ☐ 6 or 7 times
   - ☐ More than 7 times

2. Thinking about your GSDIa over the past 7 days, how would you rate your health?
   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Fair
   - ☐ Poor

3. In the past 7 days, how would you rate the severity of your GSDIa symptoms?
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

4. In the past 7 days, how bothered were you by how GSDIa impacted your life (e.g., lack of sleep, difficulty playing sports or exercising, having to follow a special diet)?
   - ☐ Not at all
   - ☐ A little
   - ☐ Somewhat
   - ☐ Quite a bit
   - ☐ Extremely

APPENDIX 7. PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

Patient Global Impression of Change (PGIC)

1. How would you rate the change in your GSDIa since the start of the study?
   - ☐ Much improved
   - ☐ Moderately improved
   - ☐ Minimally improved
   - ☐ No change
   - ☐ Minimally worse
   - ☐ Moderately worse
   - ☐ Much worse

APPENDIX 8. CTCAE TOXICITY GRADES

Refer to CTCAE Version 5.0 (DHHS, 2017) at
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.