CLINICAL STUDY PROTOCOL

IND NUMBER: 17965

EUDRACT NUMBER: 2016-003023-30

A Phase 1/2, Open-Label Safety and Dose-Finding Study 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 Number: 401GSDIA01

Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949
Sponsor Contact:	Vassili Valayannopoulos, MD Vice President, Clinical Development Ultragenyx Pharmaceutical Inc. Telephone: [redacted] Email: [redacted]
Medical Monitor:	[redacted] Associate Medical Director, Pharmacovigilance PPD Telephone: [redacted]
Version of Protocol:	7.0
Date of Protocol:	Amendment 6: 16 February 2021
Previous Versions and Dates:	Amendment 5: 28 October 2019 Amendment 4: 10 September 2019 Amendment 3: 18 February 2019 Amendment 2: 02 March 2018 Amendment 1: 13 December 2017 Version 1.0: 17 May 2017

PROTOCOL APPROVAL

Study Title	A Phase 1/2, Open-Label Safety and Dose-Finding Study 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 Number	401GSDIA01
Protocol Version	7.0
Protocol Date	Amendment 6: 16 February 2021

Protocol accepted and approved by:

Sponsor Signatory

Vassili Valayannopoulos, MD
Vice President, Clinical Development

Signature _____ Date _____

PROTOCOL AMENDMENT HISTORY AND SUMMARY OF CHANGES

The following overview summarizes significant changes to the protocol.

Version	Date	Summary of Changes
Version 1.0	07 May 2017	Original Protocol
Version 2.0	13 December 2017	An overview of changes includes the following: • Lactic acid was updated globally to lactate for consistency. Lactate testing was removed globally, with the exception of samples collected during the controlled fasting challenge (Sections 1, 2, 8.2, 8.2.6.1, 8.2.6.3, 9.1.1.2, 15.1, Table 6). • The terminology for the human and mouse gene glucose-6-phosphatase was updated globally to *G6PC* and *G6pc*, respectively. The terminology for the glucose-6-phosphatase protein was updated globally to G6Pase (Sections 1, 1.2, 1.3, 1.3.2, 6.1.1, 6.1.2, 8.3.1, 15.1, Table 6). • ClinicalTrials.gov identifiers for clinical studies with AAV8 were updated as of 11 August 2017 (Section 1.2). • It was updated that subjects in each cohort will be dosed at a minimum of 2 weeks (14 days) apart (Sections 1.3.1, 3.1, 3.2). • It was added that subjects will be informed of the long-term follow-up study during the informed consent process for this study. Additional regulations were cited regarding this process (Sections 1.3.1, 3.2.5). • It was clarified that if a stopping criterion is met, enrollment will be stopped, the data monitoring committee and regulators will be notified, and the data monitoring committee will meet (Sections 1.3.1, 3.1, 3.2.4, 9.3). • The clinical laboratory test sample types (eg, blood, serum, plasma) were removed from the protocol; this level of detail is included in the collection flow chart (Sections 1.3.1, 1.3.2, 2, 3.2.2.1, 3.2.3.3, 4.1, 4.2, 5.1, 8.1.1, 8.2.6.3, 15.1, Table 6).
		• The primary objective and endpoint were updated to explicitly state the incidence of dose-limiting toxicities at each dose level; this is a clarifying update and does not affect the content of the objective or endpoint (Sections 1.3.1, 2, 3.1). • It was clarified that dose escalation is conducted to predict the maximum tolerated dose (rather than the optimal biological dose; Sections 1.3.1, 3.1). • The maximum feasible dose of vector was updated from 7.0×10^{13} genome copies (GC)/kg to 6.5×10^{13} GC/kg in mice and the safety margin was updated to 6.5-fold in terms of actual dose and 65-fold safety margin relative to transgene expression (Section 1.3.2).

Version	Date	Summary of Changes
		• Glomerular filtration rate assessment was removed globally (Sections 2, 3.2, 3.2.2.1, 3.2.2.2, 3.2.3.3, 4.1, 8.2, 15.1, Table 6). • Magnetic resonance imaging at Week 6 was removed globally (Sections 2, 8.2, 8.1.4, 10.2.3.5, 15.1, Table 6). • Anti-G6Pase antibody testing was added as an exploratory objective and endpoint and as a safety assessment (Sections 2, 8.2, 8.2.6.9). • It was clarified that the decision to proceed to the next dosing cohort will be based on the CRM proposed dose and after the DMC has evaluated all safety data for all subjects in a dosing cohort (Section 3.1). • Text was added to allow outpatient or home study visits to be performed at a second participating study site other than the dosing site and to extend the visit duration from 1.5 hours to 1.5 to 2 hours (Section 3.2). • Figure 2 was updated to align with the Schedule of Events table. • The definition of screen failures was added (Section 3.2.1). • Text was added to allow flexibility in the personalized dinner meal before each fasting challenge (Sections 3.2.2.1, 3.2.3.3, 8.1.1, 15.1, and Table 6 [footnote x]). • Continuous glucose monitoring was removed globally (Sections 3.2, 3.2.3.3, 8.2.5, 10.2.4.5, 15.1, Table 6). • Viral shedding was replaced with vector shedding globally (Sections 3.2, 3.2.3.1, 8.1.3, 8.2.6.10, 10.2.4.7, 15.1, Table 6). • The Week 2 visit was removed globally, and inpatient study site visits were reduced accordingly from 6 to 5 (Section 3.2, 15.1, Table 6). • Text stating that laboratory values meeting stopping criteria will result in a pause in enrollment was removed. Text was added to clarify that a stopping criterion must be met for study enrollment to be suspended. Text mandating a substantial amendment if a stopping criterion is met was revised to clarify that regulatory requirements for each country will be followed (Section 3.2.4). • Specific screen failure test results that could necessitate rescreening were removed as a general statement regarding rescreening is included in Section 3.2.1 (Sections 4.1, 5.1). • Exclusion criterion #8 was updated to exclude subjects based on the presence of, or history of treatment for, hepatitis B or hepatitis C (Section 4.2). • A unique identifier was removed from the primary label (Section 6.2.1).

Version	Date	Summary of Changes
		• During the fasting challenge, it was updated that either a central or peripheral indwelling catheter may be used for sample collection (Sections 8.1.1, 8.2.6.3). • [redacted] were moved to efficacy assessments and additional details were added (Sections 8.1.3, 10.2.3.5). • Vital sign measurements were removed from 2 and 6 hours after the start of DTX401 infusion (Sections 8.2.1, 15.1, Table 6 [footnote e]). • Electrocardiograms were removed from 1 hour after the start of infusion (Sections 8.2.3, 15.1, Table 6). • A statement was added that instructions for transmitting magnetic resonance imaging results will be provided separately (Section 8.1.4).
		• The names for the [redacted] were added to Sections 8.1.3 and 15.1 and the questionnaires were added as appendices (Sections 8.1.3, 15.1, 15.3, 15.4, 15.5, Table 6). • Text on monitoring metabolic and lipid panels during steroid use was removed to allow Investigator discretion to determine the need for testing (Sections 8.2.6.1, 8.2.6.2, 15.1, Table 6). • It was added that if genotyping results were previously documented from a qualified laboratory the results can be used to satisfy the entry criteria (Section 8.3.1). • It was added that the number of hospitalizations for hypoglycemic events will be collected and recorded in the electronic case report form (Section 8.4.1). • The definition of a dose-limiting toxicity was added (Section 9.1.1.1). • The phone number for North America serious adverse event reporting was updated to [redacted] (Section 9.1.2.2). • Text was removed that stated the statistical analysis plan will be finalized prior to the start of the study (Section 10). • Detailed endpoint text was removed and a cross reference to Section 2 was added (Section 10.1). • The details of the continual reassessment method were updated to reflect the model and target toxicity (Sections 10.2, 10.2.1, 15.2). • The section entitled, Determination of the Optimal Biological Dose, and associated modeling figures were removed. • Sample size justification was added (Section 10.2.2).

Version	Date	Summary of Changes
		• The plans for adverse event presentation were updated (Section 10.2.4.1). • The statement that interim analyses will not bias the conduct of the study was removed (Section 10.2.6). • The Schedule of Events table (Table 6) was updated to reflect that eligibility criteria are confirmed on Day 0 (Section 15.1, Table 6).
		• Sample collection for clinical chemistry was removed at 0.5, 4, and 8 hours after the start of infusion (Section 15.1, Table 6 [footnote l]). • An outpatient study site or home visit was added at Day 13 (Section 15.1, Table 6). • The references were updated.
		• A STAT sample was removed from the LFT sampling at 22 hours after the start of DTX401 infusion (Section 15.1, Table 6). • Additional details related to the continual reassessment method were added (Section 15.2).
Version 3.0	02 March 2018	An overview of changes includes the following: • The Sponsor name was updated globally from Dimension Therapeutics, Inc. to Ultragenyx Pharmaceutical, Inc. • Dosing rationale text was updated to reflect updated nonclinical data (Section 1.3.2). • Instructions for treating the subject's hypoglycemia after the controlled fasting challenge were added (Sections 3.2.2.1, 3.2.3.3, 8.1.1).
Version 4.0	18 February 2019	An overview of changes includes the following: • The medical monitor name and contact information were updated (title page). • Quality of life was updated globally to health-related quality of life. • The stopping criteria for the controlled fasting challenge was updated to include symptoms of hypoglycemia (Sections 1.3.1, 3.1, 3.2.2.1, 3.2.3.3, 8.1.1, 8.2.6.3, Table 6). • It was added that subjects who withdraw early from Study 401GSDIA01 will also be offered enrollment into the extension study (Sections 1.3.1, 3.1, 3.2.5). • An exploratory objective and endpoint were added to assess the impact of DTX401 on morning glucose levels. Corresponding assessments and analyses were added (Sections 2, 8.1.3, 10.2.3.4).

Version	Date	Summary of Changes
		• A Morning Glucose Level worksheet was added to allow the subject to collect glucose levels at least 2 mornings per week throughout the study (Section 3.2, Figure 2, Table 6).
		• It was added that the controlled fasting challenge, if clinically indicated, can be performed at an unscheduled visit (Section 8.1.1, Table 6). • Details related to the magnetic resonance imaging results were added (Sections 8.1.4, 10.2.3.5). • The version of the National Cancer Institute Common Terminology Criteria for Adverse Events was updated to the most current version rather than the previously stated version number (Sections 9.1.1.1, 9.1.3, 14). • The North American toll-free safety fax number was added (Section 9.1.2.2, Table 3). • It was clarified that pregnancy complications and elective terminations for medical reasons should be reported as an AE or SAE (Section 9.2.1). • Use of cornstarch was updated from other analyses to efficacy analyses (Sections 10.2.3.3, 10.2.5). • The electronic data capture system was updated from Medidata Rave® to Oracle Health Sciences InForm (Section 10.3). • [redacted]
Version 5.0	10 September 2019	An overview of changes includes the following: • The dosing interval for subjects enrolled after completion of Cohort 2 was decreased from a minimum of 2 weeks to a minimum of 1 week (Sections 1.3.1, 3.1). • Language regarding dosing interval rationale was reorganized to aid readability (Section 1.3.1). • The starting dose for steroids for treatment of possible vector-induced hepatitis was increased from 40 mg/day to 60 mg/day (Section 8.2.6.2.1). • [redacted] • [redacted]
		• Language was added to specify that, following DTX401 administration, subjects will be discharged with prednisone to allow rapid treatment of possible

Version	Date	Summary of Changes
		vector-induced hepatitis if it occurs (Section 3.2.2.2). • The recommended target carbohydrate range of the prefasting challenge dinner meal was decreased from 20 g to 30 g to 15 g to 20 g, and the prefasting challenge cornstarch dose was decreased from 35 g to 5 g, to minimize a potential insulin spike that could result in abrupt hypoglycemia and to normalize baseline glucose levels (Sections 1.3.1, 3.2.2.1, 3.2.3.3, 8.1.1, Table 6). • Blood sample collection for measurement of glucose and lactate levels was added at the beginning of the fasting challenge to provide baseline levels (Sections 8.1.1, 8.2.6.3, Table 6). • Symptoms of hypoglycemia was removed as a fasting challenge stopping criterion (Sections 3.2.2.1, 3.2.3.3, 8.1.1). • Instructions for glucose and lactate samples collected during the fasting challenge were corrected to state that samples should be prepared and transported in accordance with the site's standard procedures (Sections 8.1.1, 8.2.6.1, 8.2.6.3). • Fasting challenge data to be captured in the eCRF was updated (Section 8.1.1). • The wording of the secondary objective was corrected (Sections 1.3.1, 3.1). • Continuous glucose monitoring was added to collect supplemental information on glucose level trends throughout the study (Sections 8.1.2, 10.2.3.2, Table 6). • The exploratory study objective and endpoint related to morning glucose level were modified to glucose level due to the addition of continuous glucose monitoring (Section 2). • Collection of blood for measurement of lipid levels was added on the morning of hospital admission for the fasting challenge (Sections 3.2.2, 3.2.3.3, 8.1.1, Table 6). • Collection of blood for measurement of cortisol, fatty acid, glucagon, insulin, and ketone levels was added at the beginning and end of the fasting challenge, or more frequently at the Investigator's discretion (Sections 3.2.2.1, 3.2.3.3, 8.1.1, 8.2.6.4, Table 6).
		• Collection of blood for measurement of cortisol levels was added approximately 1 week before the Week 12 visit (Section 8.1.1, Table 6). • The interval for liver function testing was decreased from approximately every 4 to 5 days to a minimum of

Version	Date	Summary of Changes
		every 3 to 4 days through Week 12, and liver function testing may continue beyond Week 12 if clinically indicated (Sections 3.2.3, 3.2.3.1, 8.2.6.2, Table 6). • Assessments to be completed during outpatient study site or home visits were clarified (Section 3.2.3.1). • Details regarding the collection of morning glucose levels were clarified (Section 8.1.3). • The reporting period for hypoglycemic events was clarified (Section 8.2.5, Table 6). • The table of Clinical Laboratory Parameters (Table 2) was updated for completeness (Section 8.2.6.1). • New health-related quality of life assessments (GSDIa Morning Diary, GSDIa Evening Diary, Patient Global Impression of Severity, and Patient Global Impression of Change) and a subject interview at Weeks 24 and 52 were added to guide further development of these assessments (Section 8.1.5, Table 6). • Language was added to clarify that a clinically significant change or abnormal vital sign measurement will be recorded as an AE or SAE if it is felt to be clinically significant in the medical and scientific judgment of the Investigator (Section 8.2.1). • Language was added to clarify that nonemergent hospitalization for cornstarch management or glucose monitoring during steroid administration for vector-induced hepatitis will not be considered an SAE (Section 9.1.1.3). • The reference to clinical experience with DTX401 was updated from no prior experience to limited clinical experience (Section 9.1.2.2.1). • Language was added to clarify that Investigators should rate AE intensity based on medical judgment and that the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events can be used to guide the rating of an adverse event (Section 9.1.3).
		• Language was added to clarify that, if considered clinically significant, increases in aminotransferase levels following DTX401 administration should be recorded as an AE or SAE with an event term of elevated liver function tests and graded according to the General Guidelines for Grading Events Not Captured by the CTCAE (Section 9.1.3, Table 4). • Language regarding DMC review was updated to include review at the end of the study; language regarding DMC membership was updated to reflect current DMC membership; and section content was

Version	Date	Summary of Changes
		reorganized to aid readability (Sections 1.3.1, 3.1, 9.3). • Language was added to clarify that the study will stop when the maximum sample size has been enrolled or at the Sponsor's discretion (Section 10.2.1). • Language was added to indicate that additional interim analyses may be conducted at the Sponsor's discretion (Section 10.2.6). • The Screening Period was increased from 42 days to 56 days to allow additional time for screening assessments to be completed (Section 3.2.1, Table 6). • The overall study duration was increased from 58 weeks to 60 weeks due to the increased Screening Period (Section 3.2). • Figure 2 was updated to align with modifications to the protocol. • A recommendation to collect blood samples for AAV8 neutralizing antibody testing and *G6PC* genotyping at the time written informed consent is provided was added due to the time required to analyze these samples (Sections 3.2.1, 8.2.6.6, 8.3.1, Table 6). • Screening assessments to be repeated for screen failure subjects who are rescreened were clarified (Section 3.2.1). • Recording of prior and concomitant medications, therapies, and procedures was limited to relevant information (Section 6.4). • Recording of medical history was limited to relevant information (Section 8.4.1). • The type of sample to be collected was specified (Sections 8.2.6.6, 8.2.6.7, 8.2.6.8, 8.2.6.9).
		• The frequency of assessing prescribed diet and diet intake was increased to weekly for the duration of the study (Section 8.4.2, Table 6). • The frequency of assessing prescribed cornstarch (or equivalent) and cornstarch (or equivalent) intake was increased to weekly for the duration of the study (Section 8.4.3, Table 6). • Measurement of weight was added at Weeks 6, 12, 24, and 36 (Table 6). • Magnetic resonance imaging was moved from safety assessments to efficacy assessments (Sections 8.1.4, 8.2, 10.2.3.5). • The reference to the electrocardiogram following DTX401 administration was removed (Section 3.2.2.2). This assessment was removed in Amendment 1. • Language regarding management of GSDIa was

Version	Date	Summary of Changes
		clarified (Sections 1, 1.3). • ClinicalTrials.gov identifiers for clinical studies using AAV8-mediated gene transfer was updated to include current relevant examples (Section 1.2). • The Schedules of Events were combined into 1 table, assessments were grouped by category, and the footnotes were updated to aid readability (Table 6). • The term of record retention was updated to 25 years to align with regulatory requirements (Section 12.8). • The reference list was updated (Section 14). • The protocol was reformatted, and numbering of sections, figures, and tables was updated.
Version 6.0	28 October 2019	An overview of changes includes the following: • A cohort was added to assess a prophylactic oral steroid regimen for the prevention of vector-induced hepatitis following DTX401 administration (Sections 1.3.1, 3.1). • A prophylactic oral steroid regimen was added for Cohort 4, which will be initiated on Day 1 after completion of the Day 0 controlled fasting challenge and before DTX401 administration (Sections 1.3.1, 3.1, 3.2.2.1, 8.2.6.2, 8.2.6.2.2). • Language was added to specify that Cohorts 1, 2, and 3 will receive reactive oral steroid treatment for possible vector-induced hepatitis (Sections 1.3.1, 3.1, 8.2.6.2.1).
		• Language was added to specify that, if it is necessary to modify the reactive steroid regimen, the agreed upon regimen should be documented in the subject's source documentation (Section 8.2.6.2.1). • The design rationale description was reorganized to aid readability (Section 1.3.1). • The design rationale and study overview were updated to include doses and steroid regimens administered, and outcome of DMC reviews, for Cohorts 1 and 2; doses and steroid regimens planned for Cohorts 3 and 4; and a description of modifications to the controlled fasting challenge (Sections 1.3.1, 3.1). • Language was added to clarify that blood samples for measurement of cortisol, fatty acid, glucagon, insulin, and ketone levels should be collected at the beginning and end of the fasting challenge, or more frequently at the Investigator's discretion, if possible (Sections 3.2.2.1, 3.2.3.3, 8.1.1, 8.2.6.4, Table 6). • Language was added to clarify that a blood sample for measurement of cortisol levels should be collected approximately 1 week before the Week 12 visit if

Version	Date	Summary of Changes
		possible (Section 8.1.1, Table 6). • Language was added to specify that subjects in Cohort 4 will be discharged with prednisone per the prophylactic steroid regimen (Section 3.2.2.2). • Language was added to clarify that the subject interview at Week 52 will include questions about the subject's experience in the study (Section 8.1.5, Table 6). • Language was added to clarify that prescribed diet and diet intake should be assessed during scheduled study visits and, if possible, on a weekly basis for the duration of the study (Section 8.4.2, Table 6). • Language was added to clarify that prescribed cornstarch (or equivalent) and cornstarch (or equivalent) intake should be assessed during scheduled study visits and, if possible, on a weekly basis for the duration of the study (Section 8.4.3, Table 6). • Instructions for reviewing the Morning Glucose Level monitoring worksheet were clarified (Table 6). • The timing of DMC reviews was updated (Sections 1.3.1, 9.3).
		• The sample size was increased from approximately 12 subjects to approximately 18 subjects due to the addition of Cohort 4 and the possibility to expand a cohort to confirm the findings of the cohort (Sections 3.2, 10.2.1, 10.2.2). • Language was added to clarify that the CRM model will estimate the MTD of DTX401 regardless of the steroid approach used, reactive vs prophylactic (Section 10.2.2). • Figure 2 was updated to align with modifications to the protocol. • A date field was added to the new health-related quality of life assessments and the document version was updated (Sections 15.6, 15.7, 15.8, 15.9).
Version 7.0	16 February 2021	An overview of changes includes the following: • The Sponsor Contact was changed from [redacted], MD to Vassili Valayannopoulos, MD • The sample size was decreased from approximately 18 subjects to approximately 12 subjects based on current plans to end the study after Cohort 4. (Sections 3.2, 10.2.1, 10.2.2). • The definition of euglycemia for the end of the controlled fasting challenge changed from ≥ 60 mg/dL (≥ 3.33 mmol/L) to ≥ 54 mg/dL (≥ 3.0 mmol/L).

Version	Date	Summary of Changes
		(Sections 1.3.1, 1.3.2, 2, 3.1, 3.2.2.1, 3.2.3.3, 8.1.1, 8.2.6.3, 10.2.3.1, 15.1). • The following changes were made to the controlled fasting challenge assessment (Sections 1.3.1, 3.1, 3.2.2.1, 8.1.1, 8.2.6.1, 8.2.6.3, 8.2.6.4, 15.1): o The schedule was updated to remove the CFC assessment at Week 6, and make it optional at Week 12 to ensure the safety of subjects who are taking steroids. This is a specific amendment for Cohort 4 where all subjects will be receiving a prophylactic steroid regimen between Day 0 and Week 8. Steroids can be responsible for adverse events in GSDIa patients, and require caution in any situation that could cause metabolic stress such as a fasting challenge. o The composition of the dinner meal was updated from a prespecified carbohydrate range (15–20 g) to a personalized meal for each subject, including a target carbohydrate range and overall composition in protein, fats and dietary fiber that is as close as possible to the subject's most current dinner prescription but not higher than the carbohydrate content of the dinner consumed at their baseline fasting challenge o The prefasting cornstarch dose was updated from 5 g to match the respective subject's most recent cornstarch prescription and timing post dinner o Blood sample assessments at the beginning and end of the controlled fasting challenge were updated to include cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine and ketone levels (3-hydroxy butyrate), and the instructions regarding laboratory sample collection before and during the controlled fasting challenge have been revised for clarity. o A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement has been added 30 minutes after the end of the controlled fasting challenge. o Capillary glucose measurement has been added, to be performed at the same time points as blood collection for STAT analyse.

Version	Date	Summary of Changes
		• Week 6 visit was changed to an outpatient visit, and the following assessments were removed from this visit: controlled fasting challenge (including all laboratory assessments required before and during the controlled fasting challenge), [redacted], GSDIa morning diary, GSDIa evening diary, pregnancy test (as applicable (Sections 2, 3.2, Figure 2, 3.2.3.2, 3.2.3.3, 8.1.5, 8.2.6.3, 8.2.6.4, 10.2.3.1, 15.1) • Week 12 was changed from IP to OP if the subject is still receiving prednisone at the time of the Week 12 Visit. (Section 15.1) • Language has been added to Section 8.2.6.2.2 to provide guidance on additional prednisone use after the protocol-specified prednisone taper has been competed, and guidance regarding the timing of routine vaccinations relative to prednisone use. • Targeted physical examinations were added to outpatient visits at Weeks 4, 6, and 36 (Figure 2, Section 15.1) • Language was added to specify that [redacted] will be conducted after the controlled fasting challenge is complete (Figure 2, Sections 3.2.2.1, 3.2.3.3, 8.1.4, 15.1) • The contact information for SAE and pregnancy reporting was updated (Section Sections 9.1.2.2 and Section 9.2.1) • A new section, Section 3.3, was added to address changes to the study schedule and/or study operations due to the COVID-19 pandemic. • A new section, Section 8.1.6, has been added to provide details regarding the telephone interviews that are conducted at Weeks 24 and 52. Text related to these interviews has been removed from Section 8.1.5. • The definition of dose-limiting toxicity was revised to include events based on the Sponsor's evaluation of relatedness to DTX401, as well as the Investigator's. (Section 9.1.1.1) • Text was added to specify that the dose of DTX401 in this study is in genome copies as measured by [redacted] (Section 10.2.2) • Statistical analysis methodology sections were revised and reference to the Statistical Analysis Plan added (Sections 10.2.3.2, 10.2.3.3, 10.2.3.6)

Version	Date	Summary of Changes
		• A sample for ACTH assessment was added 1 week before the Week 12 visit (in addition to cortisol) (Sections 8.2.6.4, 15.1) • Reference citations to outdated CFR, ICH GCP guidelines, and CTCAE version have been removed; this study adheres to current GCP guidance and applies current CTCAE criteria (Sections 1.3.1 3.2.5, 9.1.1.1, 9.1.3)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

Protocol Number:	401GSDIA01
Title:	A Phase 1/2, Open-Label Safety and Dose-Finding Study 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)
Sponsor:	Ultragenyx Pharmaceutical Inc. (Ultragenyx) 840 Memorial Drive Cambridge, MA 02139
Study Phase:	Phase 1/2
Sample Size:	The study is anticipated to enroll approximately 12 subjects
Study Sites:	Up to 12 global study sites
Indication:	Glycogen storage disease type Ia (GSDIa)
Primary Objective:	• To determine the safety of single intravenous (IV) doses of DTX401 in adults with GSDIa, including the incidence of dose-limiting toxicities (DLTs).
Secondary Objective:	• To establish a dose of DTX401 that achieves symptom-free euglycemia (glucose ≥ 54 mg/dL [≥ 3.0 mmol/L]) in a setting of a controlled fasting challenge to allow further clinical development.
Exploratory Objectives:	[redacted]
Primary Endpoints:	• The incidence of adverse events (AEs), including the incidence of DLTs at each dose level, treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) for each dosing cohort, assessed by severity and relationship to study product.
Secondary Endpoints:	• The change from Baseline in time (in minutes) to first hypoglycemic event (defined as glucose < 54 mg/dL [< 3.0 mmol/L]) during a controlled fasting challenge at 12, 24, and 52 weeks after IV administration of DTX401.

Exploratory Endpoints:	• [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]
Subject Population:	**Inclusion Criteria** Each subject must meet all of the following criteria at Screening to be enrolled in this study: 1. Willing and able to provide written informed consent. 2. Males and females ≥ 18 years of age. 3. Documented GSDIa with confirmation by molecular testing. 4. Documented history of ≥ 1 hypoglycemic event with glucose < 60 mg/dL (< 3.33 mmol/L). 5. Subject's GSDIa disease is stable as evidenced by no hospitalization for severe hypoglycemia during the 4-week period preceding the Screening Visit. 6. Hematology and coagulation panel results are within the normal range or, if outside the normal range, are deemed not clinically significant in the opinion of the Investigator. 7. No known allergic reaction to any component of DTX401. 8. Willing and able to comply with study procedures and requirements, including periodic inpatient hospitalization, frequent blood collections, and 24-hour urine collection.

	9. Males and females of childbearing potential must be willing to use effective contraception at the time of administration of DTX401 and for 52 weeks following administration of DTX401 to prevent the potential transmission of the AAV vector (Section 9.2.1). **Exclusion Criteria:** Subjects who meet any of the following criteria at Screening will be excluded from the study: 1. Screening or Baseline (Day 0) glucose level < 60 mg/dL (< 3.33 mmol/L); subjects may be rescreened after glucose is controlled and stable, at the discretion of the Investigator. 2. Liver transplant, including hepatocyte cell therapy/transplant. 3. Presence of liver adenoma > 5 cm in size. 4. Presence of liver adenoma > 3 cm and ≤ 5 cm in size that has a documented annual growth rate of ≥ 0.5 cm per year. 5. Significant hepatic inflammation or cirrhosis as evidenced by imaging or any of the following laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase > the upper limit of normal (ULN), total bilirubin > 1.5 × ULN, or alkaline phosphatase > 2.5 × ULN. Liver function tests may be repeated during the Screening Period at the Investigator's discretion. 6. Serum creatinine > 2.0 mg/dL. 7. Triglycerides ≥ 1000 mg/dL at the time of the Screening Visit. 8. Presence of active, or history of treatment for, hepatitis B virus or hepatitis C virus infection. 9. History of human immunodeficiency virus infection AND any of the following: CD4+ cell count < 350 cells/mm^3, change in antiretroviral therapy regimen within 6 months prior to Day 0, or viral load > 200 copies/mL, on 2 separate occasions, as measured by polymerase chain reaction. 10. History of a malignancy for which the subject has received treatment in the past 2 years except for prostate cancer treated with watchful waiting or surgically removed nonmelanoma skin cancer. 11. Active infection (viral or bacterial). 12. Anti-AAV8 neutralizing antibody titer ≥ 1:5. 13. Participation (current or previous) in another gene transfer study. 14. Participation in another investigational product study within 3 months of Screening. 15. Has a positive serum pregnancy test at Screening (females of childbearing potential only), a positive urine pregnancy test at Baseline (Day 0; females of childbearing potential only), or is nursing. 16. Has any other significant medical condition that the Investigator feels would be a risk to the subject or would impede the study.
Study Design:	This is a Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study of DTX401 in adults with GSDIa. The primary objective of the study is to determine the safety of single IV doses of DTX401, including the incidence of DLTs. The secondary objective of the study is to establish a dose of DTX401 that achieves symptom-free euglycemia (glucose ≥ 54 mg/dL [≥ 3.0 mmol/L]) in a setting of a controlled fasting challenge to allow further clinical development.

	Eligible subjects may be enrolled into 1 of the following cohorts of 3 subjects each and receive a single IV infusion of DTX401. • **Cohort 1:** Dose 1 (2.0×10^{12} genome copies [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 A cohort may be expanded to include additional subjects to confirm the findings for the cohort. Subjects in Cohorts 1 and 2 were dosed at a minimum of 2 weeks (14 days) apart. Subjects in subsequent cohorts will be dosed at a minimum of 1 week (7 days) apart. For Cohorts 1 and 2, there was a minimum of 12 weeks (84 days) between dosing of the last subject in a dosing cohort and the first subject in the next dosing cohort. After the third subject in each cohort reached the 12-week time point, the continual reassessment method (CRM) proposed a dose for the next cohort using the collected data from the previous cohort. The decision to proceed was made after the data monitoring committee (DMC) evaluated at least 12 weeks of safety data for all subjects in the dosing cohort. After reviewing Week 12 data from all subjects in Cohort 1, the DMC concluded that it was safe to enroll 3 additional subjects into Cohort 2 at Dose 2 (6.0×10^{12} GC/kg). After reviewing Week 12 data from all subjects in Cohort 2, the DMC concluded that it was safe to enroll 3 additional subjects into Cohort 3 at Dose 2 (6.0×10^{12} GC/kg) with an optimized reactive steroid regimen. An optimized reactive steroid regimen is expected to manage the elevations in liver aminotransferase levels observed in Cohorts 1 and 2 following DTX401 administration. If the optimized reactive steroid regimen does not sufficiently manage elevations in liver aminotransferase levels in Cohort 3, then Cohort 4 will be enrolled. Subjects in Cohort 4 will receive a prophylactic steroid regimen. Enrollment into Cohort 4 may begin following completion of enrollment into Cohort 3. The controlled fasting challenge was also modified following DMC review of Week 12 data from subjects in Cohort 2. To minimize a potential insulin spike that could result in abrupt hypoglycemia and normalize baseline glucose levels, the recommended target carbohydrate range of the prefasting challenge dinner meal was decreased from 20 g to 30 g to 15 g to 20 g and the prefasting challenge cornstarch dose was decreased from 35 g to 5 g. However, further analysis and review of fasting challenge data after changing the prefasting cornstarch dose to 5g showed significantly lower fasting times in cohorts 2 (W52 and W78) and 3 (W24, W32 and W52). In most instances, low post-prandial levels of blood glucose associates, persistence of high circulating insulin levels, and an inadequate adrenergic response exemplified by the absence of a cortisol increase to hypoglycemia make it challenging to interpret these results. Available CGM recordings have shown an absence of nocturnal hypoglycemia in these subjects despite an overall reduced frequency and total amount of cornstarch. The reason that several subjects can now sleep through the night at home without experiencing hypoglycemia in the absence of cornstarch consumption, but have shorter time to hypoglycemia during the inpatient fasting challenge is unclear. It could be attributed to the artificial threshold of 60 mg/dL for stopping the fasting challenge. This threshold may not allow adequate glucose release to be induced in subjects with higher insulin and lower cortisol levels. In the home setting, in the absence of prolonged fasting, subjects clearly do better as their glucose release seems to be

	better induced under their personalized dietary management, thereby preventing their glucose levels from falling to dangerous levels. With Protocol Amendment 6, the dinner meal will be personalized for each subject, and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner prescription but not higher than the carbohydrate content of the dinner consumed at their baseline fasting challenge. The prefasting cornstarch dose and time of consumption will be per the respective subject's most recent cornstarch prescription and daily regimen at home. In addition, the threshold for stopping the test was lowered to 54 mg/dL (3 mmol/L) or when the subjects present signs and symptoms of hypoglycemia. Signs and symptoms of hypoglycemia associated with an adrenergic reaction and cerebral glucopenia and most physiological hormonal and metabolic responses to hypoglycemia may not occur in these subjects until they reach these levels of blood glucose values. CGM recording during the fasting test will provide continuous glucose measurement data that will allow Investigators to closely monitor subjects when they reach the lower range of blood glucose (ie, below 60 mg/dL). Subjects enrolled in Study 401GSDIA01 will be monitored for 52 weeks following DTX401 administration. After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment into a 4-year extension study in accordance with regulatory authority regulations and ICH GCP. During the informed consent process for this study, subjects will be informed of the 4-year extension study in order to maximize subject enrollment into the extension study.
Study Methodology:	**Screening Period** After a subject has provided written informed consent and within the 56 days prior to Day 0, the Investigator or other qualified study personnel will determine if the subject is eligible for the study. This will be accomplished by reviewing the inclusion and exclusion criteria and completing all of the screening assessments. Screening assessments may be performed on more than 1 day; all assessments must be completed and results available and reviewed within the 56-day Screening Period prior to Day 0. Screening assessments include recording of the following: demographic data; medical and GSDIa history; prior medications, therapies, and procedures; vital sign measurements; and height and weight. A 12-lead electrocardiogram (ECG) and a complete physical examination will be performed. Blood samples will be collected for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus status; serum pregnancy testing (for females of childbearing potential only); *G6PC* genotyping; AAV8 neutralizing antibody testing; AAV8 binding antibody immunoglobulin G (IgG) testing; and clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, and coagulation panel). It is recommended that blood samples for *G6PC* genotyping and AAV8 neutralizing antibody testing be collected at the time written informed consent is provided. A urine sample will be collected for urinalysis. An ultrasound of the liver will be performed. Adverse events and SAEs will be monitored after the subject has provided written informed consent. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.0 mmol/L) that occurred during the previous 52 weeks will be recorded. The subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake will be recorded during scheduled study visits and, if possible, on a weekly basis through the Week 52 visit or early withdrawal. The site will provide copies of the GSDIa Morning Diary and GSDIa Evening Diary to subjects and instruct them to bring the completed assessments to the Day 0 and Weeks 12, 24, and 52 visits. The site will provide a continuous glucose monitoring (CGM) device to the subject after determining that the subject is eligible for the study. Subjects will be educated on the

	appropriate care and use of the CGM device and sensors, and instructed to wear the CGM device through the Week 52 visit or early withdrawal. **Day 0 – Baseline Assessments** Subjects will be admitted to the study site or hospital on Day 0 and discharged approximately 24 hours after administration of DTX401 (on Day 2). Each subject will remain on his or her prescribed diet for the duration of the inpatient stay. A blood sample for measurement of lipid levels will be collected on the morning of hospital admission. The sample should be collected at least 2 to 4 hours after the subject's last meal. A urine pregnancy test will be administered (for females of childbearing potential only). Blood samples will be collected for clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, and coagulation panel), AAV8 neutralizing antibody testing, AAV8 binding antibody IgG testing, cell-mediated immune response to AAV8 and G6Pase testing, and anti-G6Pase antibody testing. A urine sample will be collected for urinalysis. Saliva, urine, and stool samples will be collected to provide a baseline for assessment of vector shedding. A 12-lead ECG and a targeted physical examination will be performed. Vital sign measurements and weight will be recorded. Adverse events and SAEs will be monitored. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.0 mmol/L) that occurred since the last visit; concomitant medications, therapies, and procedures; and the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake will be recorded. Subjects will complete the [redacted] prior to invasive assessments being conducted. Subjects will complete the GSDIa Morning Diary and GSDIa Evening Diary daily for 7 days leading up to and including the Day 0 visit. Subjects will participate in a controlled fasting challenge. The Investigator or delegated sub-investigator will review the results of all laboratory assessments performed on the first day of the inpatient visit, including morning cortisol. Subjects should wear their CGM device throughout the fasting challenge, and should not change the sensor prior to the assessment. Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner dietary prescription. The content of the dinner and quantities consumed will be recorded. After dinner, subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription at approximately the same time that they typically take it, but no later than 3 hours post dinner. The time of ingestion of prefasting cornstarch and the amount consumed will be recorded. After the cornstarch is ingested, the controlled fasting challenge will begin, and the start time will be recorded accordingly. If subjects do not receive cornstarch overnight, or receive continuous overnight feedings, the fasting test will begin after they complete their dinner. Subjects will be instructed to minimize activity after they finish eating dinner until the end of the fasting challenge. During the fast, subjects may not ingest any food or drink other than water. The controlled fasting challenge will end when the subject's glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or when the subjects present signs and symptoms of hypoglycemia, or the fast reaches 15 hours without hypoglycemia, whichever occurs first. The stop time of the controlled fasting challenge will be recorded. At the end of the controlled fasting challenge, the subject's hypoglycemia should be treated per the institution's standard procedure, which may include providing the subject with a meal, cornstarch, or IV glucose, if medically indicated. Blood samples for measurement of cortisol, fatty acid, glucagon, insulin, C-peptide, growth hormone, insulin-like growth factor-binding protein 1 (IGFBP1), alanine and ketone levels

	will be collected at the beginning and end of the fasting challenge, or more frequently at the Investigator's discretion. A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Blood samples for STAT analysis of glucose and lactate will be collected per the schedule of events. Capillary glucose will also be assessed. Urine will be collected over 24 hours for the determination of total protein, microalbumin, and creatinine. The collection of urine can overlap with the controlled fasting challenge. A [redacted] will be performed after the controlled fasting challenge is complete. For subjects enrolled in Cohort 4, the Investigator will initiate a prophylactic steroid regimen after completion of the controlled fasting challenge (Section 8.2.6.2.2). **Day 1 – DTX401 Infusion** Subjects will receive a single IV infusion of DTX401. The start of the DTX401 infusion should be after all samples and procedures specified for Day 1 predose have been completed. Subjects will be discharged after a 24-hour observation period. Prior to dosing with DTX401, blood samples will be collected for clinical chemistry (including liver function tests) and vector genome determination. A 12-lead ECG will be performed, and vital sign measurements will be recorded. Adverse events and SAEs will be monitored. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.3 mmol/L) and concomitant medications, therapies, and procedures will be recorded. After dosing with DTX401, a blood sample will be collected approximately 22 hours after the start of the infusion for clinical chemistry (including liver function tests) and vector genome determination. Vital sign measurements will be recorded approximately 5 minutes after the start of the infusion and approximately 0.5, 1, 4, 8, and 22 hours after the start of the infusion. Adverse events and SAEs will be monitored. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.3 mmol/L) and concomitant medications, therapies, and procedures will be recorded. At the end of the visit, the Morning Glucose Level monitoring worksheet and instructions for completing it will be provided to the subject (Section 8.1.3). Subjects in Cohort 3 will be discharged with prednisone to allow rapid treatment of possible vector-induced hepatitis if it occurs following treatment with DTX401 (Section 8.2.6.2.1). Subjects in Cohort 4 will be discharged with prednisone per the prophylactic steroid regimen (Section 8.2.6.2.2). **Outpatient Study Site or Home Visits** Subjects will be asked to provide clinical laboratory samples at a minimum of every 3 to 4 days through Week 12 of the study, or longer if clinically indicated. Subjects may have the option of having these samples collected at their homes by clinically trained and qualified personnel (if arranged by the Investigator), unless there is a scheduled study site visit that the subject must attend in person. A blood sample will be collected for determination of clinical chemistry (including liver function tests) and sent to the central laboratory. A second blood sample will be collected for liver function tests and sent to the local laboratory (STAT sample). A blood sample will be collected for determination of cell-mediated immune response to AAV8 and G6Pase testing approximately weekly. Saliva, urine, and stool samples will be collected for assessment of vector shedding until at least 3 consecutive negative results are obtained from each sample matrix.

	Weeks 12 and 24 (Inpatient Visits) Subjects will be admitted to the study site or hospital for approximately 24 hours for all assessments. Each subject will remain on his or her prescribed diet for the duration of each inpatient stay. If the subject is off steroid treatments and the Investigator considers it is safe to proceed with the inpatient Week 12 visit, approximately 1 week before the Week 12 visit, a blood sample for measurement of ACTH and cortisol levels will be collected if possible. A blood sample for measurement of lipid levels will be collected on the morning of hospital admission at approximately the same time as collected on Day 0. The sample should be collected at least 2 to 4 hours after the subject's last meal. If the subject continues to be on steroid regimen and the Investigator determines that it is not safe to proceed with the CFC, the Week 12 visit will become an outpatient visit. Investigators should try to complete an ad hoc CFC assessment as soon as the subject has completed steroid treatment and within 8 weeks of the Week 12 visit, as an unscheduled visit. A urine pregnancy test will be performed (for females of childbearing potential only). Blood samples will be collected for clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, and coagulation panel), AAV8 neutralizing antibody testing, AAV8 binding antibody IgG testing, cell-mediated immune response to AAV8 and G6Pase testing, anti-G6Pase antibody testing (Week 12 only), and vector genome determination. A urine sample will be collected for urinalysis. A second blood sample will be collected for liver function tests and sent to the local laboratory (STAT sample) through Week 12, or longer if clinically indicated. Saliva, urine, and stool samples will be collected for assessment of vector shedding through Week 12. If still positive at the Week 12 visit, vector shedding samples will continue to be collected during scheduled study visits until at least 3 consecutive negative results are obtained from each sample matrix. A targeted physical examination will be performed. Vital sign measurements and weight will be recorded. Adverse events and SAEs will be monitored. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.3 mmol/L) that occurred since the last visit; concomitant medications, therapies, and procedures; and the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake will be recorded. If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, the subject's worksheet will be reviewed and a new worksheet will be provided to the subject. Subjects will complete the [redacted] prior to invasive assessments being conducted. Subjects will complete the GSDIa Morning Diary and GSDIa Evening Diary daily for 7 days leading up to and including each inpatient visit. Subjects will be asked to complete a brief telephone interview at Week 24 regarding their experience completing the assessments. Subjects will participate in a controlled fasting challenge. The Investigator or delegated sub-investigator will review the results of all laboratory assessments performed on the first day of the inpatient visit, including the latest cortisol values. Subjects should wear their CGM device throughout the fasting challenge, and should not change the sensor prior to the assessment. Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner dietary prescription. The content of the dinner and quantities consumed will be recorded.

	After dinner, subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription at approximately the same time that they typically take it, but no later than 3 hours post dinner. The time of ingestion of prefasting cornstarch and the amount consumed will be recorded. After the cornstarch is ingested, the controlled fasting challenge will begin, and the start time will be recorded accordingly. If subjects do not receive cornstarch overnight, the fasting test will begin after they complete their dinner. Subjects will be instructed to minimize activity after they finish eating dinner until the end of the fasting challenge. During the fast, subjects may not ingest any food or drink other than water. The controlled fasting challenge will end when the subject's glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or the subject develops signs and symptoms of hypoglycemia, or the fast reaches 15 hours without hypoglycemia, whichever occurs first. The stop time of the controlled fasting challenge will be recorded. At the end of the controlled fasting challenge, the subject's hypoglycemia should be treated per the institution's standard procedure, which may include providing the subject with a meal, cornstarch, or IV glucose, if medically indicated. Blood samples for measurement of cortisol, fatty acid, glucagon, insulin, C-peptide, growth hormone, IGFBP1, ACTH, and alanine and ketone levels will be collected at the beginning and end of the fasting challenge, or more frequently at the Investigator's discretion. A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Blood samples for STAT analysis of glucose and lactate will be collected per the schedule of events. Capillary glucose will also be assessed. Urine will be collected over 24 hours for the determination of total protein, microalbumin, and creatinine. The collection of urine can overlap with the controlled fasting challenge. An [redacted] will be performed after the controlled fasting challenge is complete. **Weeks 4, 6 and 36 (Outpatient Study Site Visits)** Blood samples will be collected for clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, and coagulation panel), AAV8 neutralizing antibody testing, AAV8 binding antibody IgG testing, cell-mediated immune response to AAV8 and G6Pase testing, and vector genome determination. A urine sample will be collected for urinalysis. A second blood sample will be collected for liver function tests and sent to the local laboratory (STAT sample) through Week 12, or longer if clinically indicated. Saliva, urine, and stool samples will be collected for assessment of vector shedding at the Week 4 visit. If still positive at the Week 24 inpatient visit, vector shedding samples will be collected during the Week 36 outpatient visit. A targeted physical examination will be performed. Vital sign measurements and weight (Week 36 only) will be recorded. Adverse events and SAEs will be monitored. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.3 mmol/L) that occurred since the last visit; concomitant medications, therapies, and procedures; and the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake will be recorded. If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, the subject's worksheet will be reviewed and a new worksheet will be provided to the subject. **End of Study (Week 52)/Early Withdrawal Visit (Inpatient Visit)** Subjects will be admitted to the study site or hospital for approximately 24 hours for all assessments. Each subject will remain on his or her prescribed diet for the duration of the inpatient stay. A blood sample for measurement of lipid levels will be collected on the

	morning of hospital admission at approximately the same time as collected on Day 0. The sample should be collected at least 2 to 4 hours after the subject's last meal. A urine pregnancy test will be performed (for females of childbearing potential only). Blood samples will be collected for clinical laboratory assessments (clinical chemistry [including liver function tests], hematology, and coagulation panel), AAV8 neutralizing antibody testing, AAV8 binding antibody IgG testing, cell-mediated immune response to AAV8 and G6Pase testing, anti-G6Pase antibody testing, and vector genome determination. A urine sample will be collected for urinalysis. Saliva, urine, and stool samples will be collected for assessment of vector shedding if samples are still positive at the Week 36 outpatient visit. A complete physical examination and a 12-lead ECG will be performed. Vital sign measurements and weight will be recorded. Adverse events and SAEs will be monitored. The number of symptomatic hypoglycemic events with documented glucose of < 60 mg/dL (< 3.3 mmol/L) that occurred since the last visit; concomitant medications, therapies, and procedures; and the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake will be recorded. If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, the subject's worksheet will be reviewed and a new worksheet will be provided to the subject. Subjects will complete the [redacted] prior to invasive assessments being conducted. Subjects will complete the GSDIa Morning Diary and GSDIa Evening Diary daily for 7 days leading up to and including the visit. Subjects will be asked to complete a brief telephone interview regarding their experience in the study and completing the assessments. Subjects will participate in a controlled fasting challenge. The Investigator or delegated sub-investigator will review the results of all laboratory assessments performed on the first day of the inpatient visit, including the latest cortisol values. Subjects should wear their CGM device throughout the fasting challenge, and should not change the sensor prior to the assessment. Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner dietary prescription. The content of the dinner and quantities consumed will be recorded. After dinner, subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription at approximately the same time that they typically take it, but no later than 3 hours post dinner. The time of ingestion of prefasting cornstarch and the amount consumed will be recorded. After the cornstarch is ingested, the controlled fasting challenge will begin, and the start time will be recorded accordingly. If subjects do not receive cornstarch overnight, the fasting test will begin after they complete their dinner. Subjects will be instructed to minimize activity after they finish eating dinner until the end of the fasting challenge. During the fast, subjects may not ingest any food or drink other than water. The controlled fasting challenge will end when the subject's glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or the subject experiences signs and symptoms of hypoglycemia, or the fast reaches 15 hours without hypoglycemia, whichever occurs first. The stop time of the controlled fasting challenge will be recorded. At the end of the controlled fasting challenge, the subject's hypoglycemia should be treated per the institution's standard procedure, which may include providing the subject with a meal, cornstarch, or IV glucose, if medically indicated. Blood samples for measurement of cortisol, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, ACTH, alanine and ketone levels will be collected at the

	beginning and end of the fasting challenge, or more frequently at the Investigator's discretion. A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Blood samples for STAT analysis of glucose and lactate will be collected per the schedule of events. Capillary glucose will also be assessed. Urine will be collected over 24 hours for the determination of total protein, microalbumin, and creatinine. The collection of urine can overlap with the controlled fasting challenge. A [redacted] will be performed after the controlled fasting challenge is complete. After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment in a 4-year extension study to evaluate the long-term (a total of 5 years) safety and efficacy of DTX401.
Treatment for Vector-Induced Hepatitis:	**Reactive Steroid Treatment for Possible Vector-Induced Hepatitis** Subjects in Cohorts 1, 2, and 3 will receive reactive oral steroid treatment for possible vector-induced hepatitis if liver aminotransferase levels increase following treatment with DTX401. The Investigator, in conjunction with the Ultragenyx medical lead, will consider starting oral steroid treatment for possible vector-induced hepatitis if a subject's ALT levels increase from the subject's baseline or recently drawn levels, and are considered by the Investigator to be possibly related to treatment with DTX401. If repeat testing is deemed necessary, every effort should be made to repeat the testing within 24 hours from receipt of test results indicating elevated levels of ALT. Based on available evidence, it is expected that vector-induced hepatitis will be self-limiting. Therefore, prednisone (or prednisolone) will be used to treat vector-induced hepatitis according to the American Association for the Study of Liver Disease guidelines, which have been modified for subjects with GSDIa so that the starting dose/duration is lower/shorter: [redacted] The Investigator, in conjunction with the Ultragenyx medical lead, may consider modifying this regimen if a subject's ALT levels do not normalize during the steroid taper. The Investigator should document the agreed upon steroid regimen in the subject's source documentation. **Prophylactic Steroid Treatment for Vector-Induced Hepatitis** Subjects in Cohort 4 will receive prophylactic oral steroid treatment to prevent possible vector-induced hepatitis. Prophylactic oral steroid regimens have been used in AAV-mediated gene transfer clinical trials for other indications (eg, Clinicaltrials.gov identifiers: NCT03223194, NCT03306277). Oral prednisone (or prednisolone) will be initiated on Day 1 following completion of the Day 0 controlled fasting challenge and before DTX401 administration as follows: [redacted]

	 The Investigator, in conjunction with the Ultragenyx medical lead, may consider modifying this regimen if a subject's ALT levels do not normalize during the steroid taper. If, in the Investigator's medical judgment, the subject may not safely tolerate initiation of oral steroid treatment on Day 1, the steroid regimen may be modified based on discussion between the Investigator and the Ultragenyx medical lead. The Investigator should document the agreed upon steroid regimen in the subject's source documentation. The Investigator may consider additional assessments or medical care, such as hospitalization or daily clinic visits, during steroid administration if, in the Investigator's medical judgment, these measures would provide additional safety benefits.
Safety Stopping Criteria:	Enrollment will be stopped and the DMC and regulators will be notified if, at any time during the study, any of the events listed below occur following administration of DTX401: • Death of a subject • An event with an intensity ≥ Grade 3 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events) develops • Occurrence of a hepatic malignancy If a stopping rule is met, enrollment will be paused and the DMC will meet to review available data. If a decision is made to resume enrollment, this decision will be communicated to and, if required, approved by regulatory authorities according to country requirements. An event that meets any of the above criteria will be reported immediately and captured as an AE/SAE in the electronic case report form by the study site. If a stopping criterion is met and study enrollment is suspended, all subjects who have been enrolled will remain in the study and will continue to be monitored through their completion or withdrawal from the study.
Efficacy Assessments:	Efficacy assessments include the following: the change from Baseline in time (in minutes) to first hypoglycemic event (defined as glucose < 54 mg/dL [< 3.0 mmol/L]) during a controlled fasting challenge at 12, 24, and 52; cornstarch intake; glucose level trends; morning glucose levels; [redacted]; and [redacted].
Safety Assessments:	Safety assessments include the following: AEs, SAEs, vital sign measurements, complete and targeted physical examination findings, ECG results, documented 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 IgG, assessment of any cell-mediated immune response to AAV8 and G6Pase, and measurement of anti-G6Pase antibodies.

Estimated Study Duration:	The duration of the study for each subject is defined as the date the subject provides written informed consent through the Week 52 visit. Subjects will be in the study for approximately 60 weeks (including the Screening Period). After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment into a 4-year extension study to evaluate the long-term (for a total of 5 years) safety and efficacy of DTX401.
Study Product, Dose, and Route of Administration:	DTX401 will be administered as a single peripheral IV infusion. The following doses may be evaluated using a CRM to estimate the maximum tolerated dose (MTD) of DTX401 regardless of the steroid approach used (ie, reactive vs prophylactic): **Dose 1:** 2.0×10^{12} GC/kg **Dose 2:** 6.0×10^{12} GC/kg **Dose 3:** 1.0×10^{13} GC/kg
Statistical Methods:	**Determination of the Maximum Tolerated and Optimal Biological Doses** The optimal biological dose (OBD) will be based on the MTD and an assessment of clinical benefit. A CRM will be used for dose escalation to estimate the MTD of DTX401. The CRM uses the Bayesian method to model the probability of experiencing a DLT for each given dose in order to recommend the dose for the next cohort. The CRM will evaluate subjects based on the dose administered regardless of the steroid approach used (ie, reactive vs prophylactic). A DLT is defined as any AE/SAE ≥ Grade 3 that is considered by the Investigator and/or Sponsor to be related to DTX401. The MTD is defined as the highest dose where the predicted probability of experiencing a DLT is less than or equal to the target toxicity rate. In this study, the target toxicity rate is 0.25. **Interim Analysis** An interim analysis will be conducted when a minimum of 12-week data are available for all subjects from at least 2 dosing cohorts. Additional interim analyses may be conducted at the Sponsor's discretion. **Safety Analyses** All statistical analyses of safety outcomes will be descriptive, with the exception of the CRM modelling. The incidence of AEs and TEAEs will be summarized for each dose by system organ class and preferred term. Additionally, TEAEs may be summarized for each dose by severity and relationship to study product, if applicable. SAEs will be presented for each dose by relationship to study product. Summary tables will present the total numbers of TEAEs as well as the number of subjects with TEAE incidence by system organ class and preferred term. Subjects experiencing an event more than once with varying severity will be counted only once in the maximum severity within each system organ class and preferred term. For incidence of relationship to study product, subjects will be counted only once in the category of the strongest relationship to study product within each system organ class/preferred term. Other safety data, including vital sign measurements, complete and targeted physical examination findings, ECG results, documented symptomatic hypoglycemic events, clinical laboratory data, vector shedding, vector genome determination, measurement of neutralizing antibody titer to AAV8, measurement of AAV8 binding antibody IgG, assessment of any cell mediated immune responses to AAV8 and G6Pase, and measurement of antiG6Pase antibodies will be summarized.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

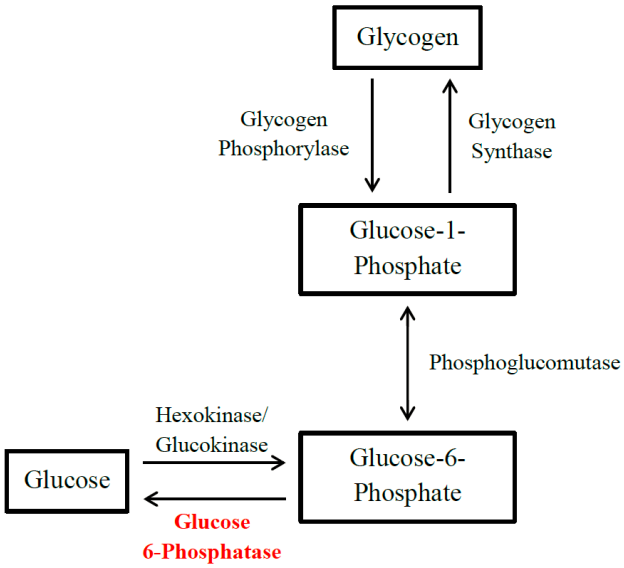
Abbreviation	Definition
AAV	adeno-associated virus
AAV2	adeno-associated virus serotype 2
AAV8	adeno-associated virus serotype 8
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CRM	continual reassessment method
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
[redacted]	[redacted]
FDA	US Food and Drug Administration
G6P	glucose-6-phosphate
G6Pase	glucose-6-phosphatase (protein)
G6PC	glucose-6-phosphatase (gene)
G6pc$^{-/-}$	glucose-6-phosphatase knockout mice
GC	genome copies
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSDIa	glycogen storage disease type Ia
HCA	hepatocellular adenoma
HCC	hepatocellular carcinoma
[redacted]	[redacted]
IBC	institutional biosafety committee
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	independent ethics committee
IGFBP1	insulin-like growth factor-binding protein 1
IgG	immunoglobulin G
IRB	institutional review board
IV	Intravenous
MED	minimal effective dose
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MTD	maximum tolerated dose
NCI	National Cancer Institute
OBD	optimal biological dose
PVG	pharmacovigilance
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	serious, unexpected, suspected adverse drug reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. INTRODUCTION

Glucose-6-phosphatase is a glucose-6-phosphate (G6P) hydrolase located in the endoplasmic reticulum that is primarily expressed in the liver, kidneys, and intestine. It is a highly hydrophobic protein with 9 transmembrane domains (Pan et al., 1998). The amino and carboxyl termini of the glucose-6-phosphatase (G6Pase) protein are located on opposite sides of the endoplasmic reticulum membrane, with the active site of the enzyme facing the endoplasmic reticulum lumen (Lei et al., 1993; Lei et al., 1995b; Lei et al., 1995c). Glucose-6-phosphatase is responsible for catalyzing the terminal step in hepatic and renal glycogenolysis and gluconeogenesis (Figure 1): the hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate provides a significant amount of circulating glucose (Foster and Nordlie, 2002). In patients with glycogen storage disease type Ia (GSDIa), free glucose molecules are not generated for export into the body's circulation, and as a result, glucose from glycogen stores is unavailable during periods of fasting, resulting in severe hypoglycemia. The excess glucose-6-phosphate molecules are shunted toward the production of triglycerides (eventually stored as fat) and the pentose-phosphate pathway (leading to increased uric acid production). Additionally, during periods of prolonged hypoglycemia, an increased rate of glycolysis and catabolism of muscle and fats results in a build-up of lactate (Chou and Mansfield, 1999; Chou, 2001; van Schaftingen and Gerin, 2002).

Figure 1: Overview of Glycogenesis and Glycogenolysis



Glycogen storage disease type Ia, also known as von Gierke disease, is a severe autosomal recessive inborn error of metabolism that is caused by mutations of the *G6PC* gene located on chromosome 17q21 (Lei et al., 1993; Chou, 2001). Patients with GSDIa present with severe hypoglycemia and seizures at a few months of age. Like many other inherited disorders, GSDIa can be readily detected by screening a bloodspot sample for one of several common mutations (Lei et al., 1995a). The importance of diagnosing and treating GSDIa early is emphasized by the severe complications that arise when the disease is left untreated, including life-threatening hypoglycemia, severe lactic acidosis, growth failure, renal Fanconi syndrome, and pancreatitis. Acute complications of GSDIa, such as hypoglycemia, severe metabolic acidosis, and renal

tubular- dysfunction, respond favorably to and can be prevented with strict dietary restrictions and frequent consumption of uncooked cornstarch. However, these restrictions have significant limitations and require constant vigilance to avoid acute metabolic decompensation that is accompanied by life-threatening hypoglycemia and lactic acidosis. In addition, dietary restrictions are often not an effective means of preventing the long-term clinical complications associated with GSDIa, including proteinuria (that may progress to renal failure), growth retardation, osteopenia, and the formation of hepatocellular adenomas (HCAs) and hepatocellular carcinomas (HCCs) (Chen et al., 1988; Wolfsdorf and Crigler, 1997; Wolfsdorf et al., 1997; Wolfsdorf et al., 1999).

Complications, such as hepatomegaly (resulting from the pathological accumulation of glycogen in the liver), an increase in the number and size of HCAs, and the development of HCCs become more common as individuals with GSDIa age (Franco et al., 2005). For example, HCAs are present in 70% to 80% of GSDIa patients over the age of 25 years (Lee et al., 2012), with up to 10% of HCAs developing into life--threatening HCCs (Franco et al., 2005; Reddy et al., 2007; Lee et al., 2012). Orthotopic liver transplantation has become a treatment option for patients and has been shown to correct hypoglycemia and other biochemical abnormalities associated with GSDIa, as well as result in an increase in body height (Matern et al., 1999; Boers et al., 2014). These results provide evidence for the efficacy and benefit of restoring *G6PC* expression in the liver of patients with GSDIa. However, given that liver transplantation is limited by donor availability and is associated with significant risk of morbidity and mortality including a very high rate of renal failure (Davis and Weinstein, 2008; Boers et al., 2014), there is a significant unmet medical need for a treatment that allows for sustained euglycemia and prevention of the long-term complications and life-threatening hypoglycemia that are associated with GSDIa. In nonclinical studies, adeno-associated virus (AAV) serotype 8-mediated delivery of *G6PC* in mice and dogs with GSDIa has restored G6Pase activity and ameliorated disease sequelae (Koeberl et al., 2008; Koeberl et al., 2009; Weinstein et al., 2010; Chou and Mansfield, 2011), providing evidence that gene transfer could have significant benefit in patients with GSDIa.

1.1. Adeno-Associated Viral Vectors

Adeno-associated virus is a nonenveloped, icosahedral, single-stranded DNA virus. Given that wild-type AAV displays wide tissue tropism and is capable of persisting in tissues for long durations without pathogenic effects, the use of recombinant AAV vectors has become a popular tool for gene delivery. Additionally, recombinant AAV vectors are nonreplicating and the vector genomes exist as an episome following tissue transduction, minimizing the risk of insertional mutagenesis (Nakai et al., 2001). Since the first genetic engineering of wild-type AAV as a gene delivery vector in the early 1980s, recombinant AAV has shown great promise as an effective and safe gene delivery vehicle for treatment of diseases (Gao et al., 2005; Mingozzi and High, 2011).

Adeno-associated virus serotype 2 (AAV2) was the first AAV that was used for gene transfer applications and has been used in numerous studies for a variety of diseases such as alpha 1-antitrypsin deficiency, Batten disease, and cystic fibrosis (Mingozzi and High, 2011). In animal models, AAV2-mediated gene transfer was shown to treat the underlying disease for many years (Snyder et al., 1999; Mount et al., 2002; Wang et al., 2005; Nichols et al., 2010).

However, in humans, AAV2-mediated delivery was either subtherapeutic or only lasted a few months (Manno et al., 2003; Manno et al., 2006). This was attributed to several limitations of AAV2 vectors including low transduction efficiency (Yan et al., 2002), high seroprevalence of neutralizing antibodies against AAV2 in humans (Boutin et al., 2010), and potentially destructive T-cell responses to capsids (Gao et al., 2009; Vandenberghe et al., 2006; Wang et al., 2007). There has also been evidence of B-cell responses against the transgene product in an animal model of hemophilia (Herzog et al., 2001).

1.2. Selection of the AAV Clinical Candidate

The host immune response (ie, neutralizing antibodies and T-cell responses) limiting the efficacy of AAV2-mediated gene transfer (Section 1.1) was not predicted in the initial animal studies, due to AAV2 not being endemic to the nonhuman species under investigation. Novel AAV serotypes, isolated from nonhuman primates, are divergent enough from endemic human serotypes to circumvent the neutralizing antibodies that exist in most humans while retaining similar tissue tropism (Gao et al., 2002).

One of these serotypes, AAV serotype 8 (AAV8), displays strong tropism for the liver (Gao et al., 2002) and has been tested extensively as a vector for gene transfer in nonclinical and clinical models of hemophilia (Davidoff et al., 2005; Jiang et al., 2006; Nathwani et al., 2011b; Nathwani et al., 2006; Nathwani et al., 2007).

These studies have shown that AAV8 has clear advantages over AAV2 including excellent transduction efficiency; liver-specific tropism; stable transgene expression; a lack of hepatotoxicity as measured by peak serum aminotransferases; a lack of liver histopathology; a lack of T-cell activation to the transgene product; and low levels of pre-existing neutralizing antibodies in humans, minimizing their inhibition of in vivo transduction. Furthermore, AAV8 has shown impressive efficacy and safety in clinical studies for hemophilia B (Nathwani et al., 2011b; Nathwani et al., 2014) and is being studied in multiple indications, including hemophilia A (ClinicalTrials.gov identifier: NCT03001830, NCT03370172), hemophilia B (ClinicalTrials.gov identifiers: NCT00979238, NCT01687608), late-onset ornithine transcarbamylase deficiency (ClinicalTrials.gov identifier: NCT02991144), Pompe disease (ClinicalTrials.gov identifier: NCT03533673), and Crigler-Najjar syndrome (Clinicaltrials.gov identifier: NCT03223194). The study product, DTX401, contains a codon-optimized human wild-type *G6PC* with expression driven by both the native *G6PC*-specific promoter and enhancer elements encapsidated within a nonreplicating recombinant AAV8 vector. In *G6pc* knockout (*G6pc* $^{-/-}$) mice, a vector similar to DTX401 showed a sustained, dose-dependent improvement in plasma glucose levels following a single intravenous (IV) injection that was similar to the improvement in wild-type mice (Yiu et al., 2010; Lee et al., 2012). Furthermore, restoring G6Pase activity (from 3% to 63% of wild-type levels) prevented the formation of HCA for up to 90 weeks, which had previously been reported in a liver-specific knock out model (Mutel et al., 2011; Lee et al., 2012). These data provide support for the feasibility of this therapeutic approach in humans.

DTX401 offers the following advantages for patients with GSDIa:

- The liver is a natural site of G6Pase synthesis. The AAV8 serotype demonstrates high liver tropism and can achieve efficient liver gene transfer following IV infusion (Gao et al., 2002).
- The AAV8 serotype is not thought to be endemic in the human population; therefore, the prevalence of neutralizing antibodies to AAV8 that would prevent efficient transduction of the liver is expected to be low in patients with GSDIa (Calcedo and Wilson, 2013).

1.3. Study Rationale

The use of gene transfer for treating GSDIa in *G6pc*$^{-/-}$ mice and in a naturally occurring canine model of GSDIa has been tested using both adenoviral (murine model only) (Koeberl et al., 2007) and AAV delivery systems (both murine and canine models) (Beaty et al., 2002; Sun et al., 2002; Ghosh et al., 2006; Koeberl et al., 2006; Koeberl et al., 2008; Chou and Mansfield, 2007; Kishnani et al., 2010; Yiu et al., 2010; Chou and Mansfield, 2011; Lee et al., 2012). These studies demonstrated long-term correction of the disease sequelae, including correction of fasting hypoglycemia; reduction of uric acid, triglycerides, and cholesterol; improved growth; reduction in hepatomegaly and nephromegaly; and a reduction in lactic acidosis (canine model). Histologically, there was also a reduction in glycogen deposition in the liver, and recent data demonstrated prevention of both HCAs and HCCs (Lee et al., 2012).

Glucose-6-phosphatase gene transfer is expected to be effective for the treatment of GSDIa because the disease is caused by mutations within a single gene (Lei et al., 1995a; Lei et al., 1993; Chou, 2001). Currently, no gene transfer product has been approved for the treatment of GSDIa. Based on previous clinical experience with AAV8, DTX401 is expected to result in sustained (at least 3 years following vector infusion) expression of *G6PC* (Nathwani et al., 2011b; Nathwani et al., 2014). Therefore, unlike current treatment options (ie, strict dietary restrictions and frequent consumption of uncooked cornstarch), *G6PC* gene transfer offers the potential to correct the underlying deficiency for a prolonged period of time with a single IV infusion. Furthermore, increasing G6Pase activity should allow patients with GSDIa to avoid hypoglycemic episodes and long-term complications associated with GSDIa, which should greatly improve their health-related quality of life (HRQoL).

1.3.1. Design Rationale

The design of this first-in-human study is consistent with global regulatory guidelines for protocol design, including subject selection, dose estimation, precautions applied between dosing cohorts, risk mitigation, and study stopping criteria.

Study 401GSDIA01 is a Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study to determine the safety, tolerability, and efficacy of DTX401 in adults with GSDIa. The primary objective of the study is to determine the safety of single IV doses of DTX401, including the incidence of dose-limiting toxicities (DLTs). The secondary objective of the study is to establish a dose of DTX401 that achieves symptom-free euglycemia (glucose ≥ 54 mg/dL

[≥ 3.0 mmol/L]) in a setting of a controlled fasting challenge to allow further clinical development.

Patients with GSDIa will typically develop hypoglycemia within 2 to 4 hours of a meal in the absence of treatment (ie, cornstarch) (Bali et al., 2016). Ingestion of uncooked or modified cornstarch has been shown to maintain glucose above 3.0 mmol/L for up to 10 hours (median 7 hours) in patients with GSDIa during a controlled fasting challenge (Bhattacharya et al., 2007); however, there are limited data to estimate intraperson variability in time to reaching hypoglycemia. Patients with GSDIa have a more consistent fasting profile than patients with other glycogen storage diseases (Wolfsdorf et al., 1999). Therefore, a conservative estimate for intraperson variability would be ± 2 hours. In this study, subjects will be administered a 5 g oral dose of cornstarch just prior to starting the controlled fasting challenge. This dose of cornstarch is expected to minimize a potential insulin spike following dinner that could result in abrupt hypoglycemia, normalize baseline glucose values, allow subjects to fast for a few hours, and minimize intraperson variability. In nonclinical studies, *G6pc*$^{-/-}$ mice were able to survive a 24-hour fast following treatment with a vector similar to DTX401 (Lee et al., 2012). Based on these data, it is expected that DTX401 gene transfer should prevent hypoglycemia for at least 8 hours during the controlled fasting challenge. This clinically meaningful change from baseline (ie, 2 to 4 hours (Bali et al., 2016)) would represent a clear efficacy signal outside an effect that can be attributed to anticipated intraperson variability (ie, ± 2 hours).

Eligible subjects will be enrolled into cohorts of 3 subjects each and receive a single IV infusion of DTX401. Subjects in Cohorts 1 and 2 were dosed at a minimum of 2 weeks (14 days) apart. Subjects in subsequent cohorts will be dosed at a minimum of 1 week (7 days) apart.

The proposed dosing interval of 14 days between subjects in Cohorts 1 and 2, followed by a dosing interval of 7 days in subsequent cohorts, is supported by the safety profile and lack of serious adverse reactions reported in AAV-mediated gene transfer in human subjects, including a hemophilia B clinical study using an AAV8 vector (Manno et al., 2006; Nathwani et al., 2011b; Nathwani et al., 2014) and this study (Derks et al., 2019; Weinstein et al., 2019). Moreover, a Phase 1/2 clinical study in hemophilia B that used AAV-mediated gene transfer at a starting dose of 5.0×10^{12} genome copies (GC)/kg (higher than the proposed DTX401 starting dose of 2.0×10^{12} GC/kg) at multiple European study sites dosed subjects within a cohort at a minimum of only 1 day (24 hours) apart (uniQure, 2014)(Clinicaltrials.gov identifier: NCT02396342; EudraCT Number: 2013-005579-42).

The most common product-related adverse event (AE) observed in clinical studies with AAV-mediated gene transfer to subjects with moderate to severe hemophilia B has been an asymptomatic transient increase in liver aminotransferase levels (though still within the normal reference range for these laboratory parameters) and concurrent decline in transgene expression approximately 7 to 10 weeks following vector administration (Manno et al., 2006; Nathwani et al., 2011b; Nathwani et al., 2014). In all cases, the transient increase in liver aminotransferase levels resolved without clinical sequelae. It has been hypothesized that this vector-induced hepatitis is due to the activation of capsid-specific cytotoxic T lymphocytes and destruction of transduced liver cells (Mingozzi et al., 2007). As this is the only identified AE with AAV gene transfer, and given that subjects in this study will be closely monitored for vector-induced

hepatitis and treated with corticosteroids if needed (Section 8.2.6.2), having an interval of more than 14 days between subjects in Cohorts 1 and 2 and more than 7 days between subjects in subsequent cohorts does not change either safety evaluations or the medical management of study subjects. To date, no related serious adverse events (SAEs) or DLTs have been reported for DTX401. Consistent with previous experience (Manno et al., 2006; Nathwani et al., 2011b; Nathwani et al., 2014), mild, transient, asymptomatic increases in liver aminotransferase levels have been observed following DTX401 administration that resolved with steroids (Derks et al., 2019; Weinstein et al., 2019).

Subject safety will be closely monitored throughout the study, including assessment of hypoglycemic events, frequent monitoring of liver enzymes, and inpatient observation following dosing and at multiple time points throughout the 52-week study duration.

For Cohorts 1 and 2, there was a minimum of 12 weeks (84 days) between dosing of the last subject in a dosing cohort and the first subject in the next dosing cohort. After all subjects in Cohorts 1 and 2 completed Week 12, the continual reassessment method (CRM) proposed a dose for the next cohort using the collected data from the previous cohort. The DMC met to review safety data (ie, AEs/SAEs, physical examination findings, vital sign measurements, electrocardiogram [ECG] results, and clinical laboratory assessments [including assessment of liver function]) and provide a recommendation for progressing to the next dosing level (Section 9.3). The CRM will be used for dose escalation to estimate the maximum tolerated dose (MTD) of DTX401 (Section 10.2.1).

After reviewing Week 12 data from all subjects in Cohort 1, the DMC concluded that it was safe to enroll 3 additional subjects into Cohort 2 at Dose 2 (6.0×10^{12} GC/kg). After reviewing Week 12 data from all subjects in Cohort 2, the DMC concluded that it was safe to enroll 3 additional subjects into Cohort 3 at Dose 2 (6.0×10^{12} GC/kg) with an optimized reactive steroid regimen. An optimized reactive steroid regimen is expected to manage the elevations in liver aminotransferase levels observed in Cohorts 1 and 2 following DTX401 administration. If the optimized reactive steroid regimen does not sufficiently manage elevations in liver aminotransferase levels in Cohort 3, then Cohort 4 will be enrolled. Subjects in Cohort 4 will receive a prophylactic steroid regimen. Enrollment into Cohort 4 may begin following completion of enrollment into Cohort 3 (Section 3.1).

In Cohort 4, oral prednisone (or prednisolone) will be initiated on Day 1 after completion of the Day 0 controlled fasting challenge and before DTX401 administration, sustained for 4 weeks, and then tapered (Section 8.2.6.2.2). Prophylactic oral steroid regimens have been used in AAV-mediated gene transfer clinical trials for other indications (eg, Clinicaltrials.gov identifiers: NCT03306277, NCT03223194).

The controlled fasting challenge was also modified following DMC review of Week 12 data from subjects in Cohort 2. To minimize a potential insulin spike that could result in abrupt hypoglycemia and normalize baseline glucose levels, the recommended target carbohydrate range of the prefasting challenge dinner meal was decreased from 20 g to 30 g to 15 g to 20 g and the prefasting challenge cornstarch dose was decreased from 35 g to 5 g.

However, further analysis and review of fasting challenge data after changing the prefasting cornstarch dose to 5g showed significantly lower fasting times in cohorts 2 (W52 and W78) and 3 (W24, W32 and W52). In most instances, low post-prandial levels of blood glucose associates, persistence of high circulating insulin levels, and slow cortisol response to hypoglycemia make it challenging to interpret these results. Available CGM recordings have shown an absence of nocturnal hypoglycemia in these subjects despite an overall reduced frequency and total amount of cornstarch. The reason that several subjects can now sleep through the night at home without experiencing hypoglycemia in the absence of cornstarch consumption, but have shorter time to hypoglycemia during the inpatient fasting challenge is unclear. It could be attributed to the artificial threshold of 60 mg/dL for stopping the fasting challenge. This threshold may not allow adequate glucose release to be induced in subjects with higher insulin and lower cortisol levels. In the home setting, subjects clearly do better as their glucose release seems to be better induced, thereby preventing their glucose levels from falling to dangerous levels.

With Protocol Amendment 6, the dinner meal will be personalized for each subject, and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner prescription but not higher than the carbohydrate content of the dinner consumed at their baseline fasting challenge. The prefasting cornstarch dose and time of consumption will be per the respective subject's most recent cornstarch prescription and daily regimen at home. In addition, the threshold for stopping the test was lowered to 54 mg/dL (3.0 mmol/L) or when the subject experiences signs and symptoms of hypoglycemia. The new threshold is justified by the fact that signs and symptoms of hypoglycemia associated with an adrenergic reaction and cerebral glucopenia and most physiological hormonal and metabolic responses responses to hypoglycemia may not occur in GSDIa subjects until they reach these levels of blood glucose values. CGM recording during the fasting test will provide continuous glucose measurement data that will allow Investigators to closely monitor subjects when they reach the lower range of blood glucose (ie, below 60 mg/dL).

The DMC will meet at the end of the study and may, at any time, recommend modifying or pausing enrollment due to safety concerns based on their periodic data reviews. Additionally, if an Investigator reports an AE/SAE that meets any of the safety stopping criteria (Section 3.2.4), enrollment will be paused and the DMC will meet to review available data. If a decision is made to resume enrollment, this decision will be communicated to and, if required, approved by regulatory authorities according to country requirements. The full scope of each DMC review will be outlined in the DMC charter.

AAV vectors represent a class of viral vectors that are nonreplicating, nonintegrating, and present a low risk for gene therapy-related delayed adverse reactions. Recommended long-term safety monitoring for subjects enrolled in AAV gene therapy clinical trials is a minimum of 5 years (FDA, 2006; CHMP, 2009).

Subjects enrolled in Study 401GSDIA01 will be monitored for 52 weeks following DTX401 administration. After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment into a 4-year extension study in accordance with regulatory authority regulations and ICH GCP. During the informed consent process for this study, subjects will be

informed of the 4-year extension study in order to maximize subject enrollment into the extension study.

1.3.2. Dosing Rationale

The clinical target for DTX401 is to achieve euglycemia in the fasting state (defined as glucose ≥ 54 mg/dL [≥ 3.0 mmol/L]). The determination of a clinical starting dose is based on available nonclinical data with DTX401, including the minimal effective dose (MED) and optimal effective dose of DTX401 in mice, clinical experience with other AAV8 products, and known limitations when scaling between species.

To provide information to support the selection of a safe clinical starting dose, Ultragenyx Pharmaceutical Inc. (Ultragenyx) conducted a pharmacology proof-of-concept efficacy study in *G6pc*$^{-/-}$ mice to characterize the biological activity of 2 different transgenes in an animal model of GSDIa and a Good Laboratory Practice (GLP) toxicity and biodistribution study in male and female wild-type C57 black 6 (C57BL/6) mice.

In order to estimate the allometric scaling needed for AAV8-mediated delivery of the *G6PC* transgene in this study between mice and humans, the following 2 data sets using AAV-mediated transfer of human factor IX were examined: the uniQure data set (Amsterdam, The Netherlands) (uniQure, 2015; uniQure, 2016) and the Nathwani data set (Nathwani et al., 2007; Nathwani et al., 2011a; Nathwani et al., 2011b). The AAV serotype 5 vector used in the uniQure studies was shown to have a 10-fold scaling between mouse and human (uniQure, 2015; uniQure, 2016). The AAV8 vector used in the Nathwani studies supports a 10-fold scaling from mouse to nonhuman primates and a 4-fold scaling between nonhuman primates and humans, for a total of 40-fold between mouse and human (Nathwani et al., 2007; Nathwani et al., 2011a; Nathwani et al., 2011b). Therefore, when considering a clinical dosing rationale, in light of the available comparison data between mice and humans, it seems reasonable to consider a 10- to 40-fold increase in dose from mice to humans to achieve similar target levels for the expression and activity of G6Pase. The MED for DTX401 was 5×10^{11} GC/kg in neonatal *G6pc*$^{-/-}$ mice that were observed for a 2-week period. Due to the growth of the animals during this time, vector dilution in the liver also needs to be considered and was estimated to be approximately 2.5- to 5-fold (Wang et al., 2012). Similar results were reported in *G6pc*$^{-/-}$ mice treated at 2 weeks of age, where there was an approximate 2.7-fold decrease in G6Pase activity between 4 and 6 weeks after dosing (from 243.3% to 87.6% of wild-type activity) (Yiu et al., 2010). Therefore, both the increase in dose due to allometric scaling from mice to humans and vector dilution were considered when choosing candidate doses of DTX401 for this study. The use of these correction factors provides a range for the potential MED in humans (Table 1). The minimum dose that could provide benefit in humans is estimated to fall between 1.0×10^{12} GC/kg (ie, a 2-fold increase) and 8.0×10^{12} GC/kg (ie, a 16-fold increase).

Table 1: Allometric Scaling and Dilution Factors for Determining the Minimal Effective Dose of DTX401 in Humans

Mouse MED (GC/kg)	Mouse to NHP/Human Conversion Factor	Human Dose (GC/kg)	Dilution Factor (Neonate to Adult Mouse)	Corrected Human Dose (GC/kg)
5×10^{11}	× 10	5×10^{12}	5	1×10^{12} (minimum)
5×10^{11}	× 10	5×10^{12}	2.5	2×10^{12}
5×10^{11}	× 40	2×10^{13}	5	4×10^{12}
5×10^{11}	× 40	2×10^{13}	2.5	8×10^{12} (maximum)

Abbreviations: GC = genome copies; MED = minimal effective dose; NHP = nonhuman primate.

In comparison to the clinical development of traditional small molecule and biologic therapies, clinical studies for AAV-mediated gene transfer have an additional consideration: after initial dosing, it is expected that subjects who are administered DTX401 will develop neutralizing antibodies to AAV8 and will likely receive limited benefit from subsequent dosing with this vector. Therefore, unlike classic dose-escalation studies, there is a greater focus on targeting efficacy in addition to safety. Taking into consideration the uncertainty in projecting a human dose, as noted in the US Food and Drug Administration (FDA) guidance (FDA, 2015), a dose of 2.0×10^{12} GC/kg, which is twice the minimum projected human MED (1.0×10^{12} GC/kg), was selected as the starting dose for the Phase 1/2 study (Table 1). This dose is expected to provide a reasonable chance for study subjects to achieve a clinically meaningful normalization of glucose and will provide critical safety information in humans for DTX401.

A standard approach for dose finding in gene transfer studies is to adjust the dose (up or down) in half-log increments; therefore, if 2.0×10^{12} GC/kg is projected to provide G6Pase activity at the minimum level to prevent hypoglycemia, a dose that is a half-log more is 6.0×10^{12} GC/kg. The highest clinical dose planned is 1.0×10^{13} GC/kg. The candidate doses of 2.0×10^{12} GC/kg, 6.0×10^{12} GC/kg, and 1.0×10^{13} GC/kg in this study (Study 401GSDIA01) are also being studied in the DTX301 Phase 1/2 clinical study (Study 301OTC01) for ornithine transcarbamylase, another gene transfer study in an inborn error of metabolism condition, based on similar allometric scaling derived from mouse MED data.

Based on existing safety data from clinical studies using AAV-mediated gene transfer (including multiple hemophilia programs), substantial toxicity in the predicted therapeutic range is not anticipated. Ultragenyx is also taking into account the amount of DTX401 Chemistry, Manufacturing, and Controls material that can be produced over the anticipated timeline of this Phase 1/2 study and the maximal feasible dose of vector that can be administered to mice in GLP toxicology studies (based on dose volume and concentration of vector). Assuming that an MTD is not identified in nonclinical studies, the proposed dose-finding approach for this Phase 1/2 study is consistent with the FDA Guidance for Industry on the Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, which indicates that achieving a specified target range of exposure is the focus of a cellular or gene therapy program when “there are significant practical limits of the dose of the product that can be produced or delivered” (FDA, 2015).

For additional nonclinical information, please refer to the DTX401 Investigator’s Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To determine the safety of single IV doses of DTX401 in adults with GSDIa, including the incidence of DLTs.	The incidence of AEs, including the incidence of DLTs at each dose level, TEAEs, and SAEs for each dosing cohort, assessed by severity and relationship to study product.
Secondary	
To establish a dose of DTX401 that achieves symptom-free euglycemia (glucose ≥ 54 mg/dL [≥ 3.0 mmol/L]) in a setting of a controlled fasting challenge to allow further clinical development.	The change from Baseline in time (in minutes) to first hypoglycemic event (defined as glucose < 54 mg/dL [< 3.0 mmol/L]) during a controlled fasting challenge at 12, 24, and 52 weeks after IV administration of DTX401.
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objective	Endpoint
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: AAV8 = adeno-associated virus serotype 8; AE = adverse event; DLT = dose-limiting toxicity; [redacted] G6Pase = glucose-6-phosphatase; GSDIa = glycogen storage disease type Ia; [redacted]; IV = intravenous; [redacted] SAE = serious adverse event; TEAE = treatment-emergent adverse event.

3. INVESTIGATIONAL PLAN

3.1. Study Overview

Study 401GSDIA01 is a Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study to determine the safety, tolerability, and efficacy of DTX401 in adults with GSDIa. The primary objective of the study is to determine the safety of single IV doses of DTX401, including the incidence of DLTs. The secondary objective of the study is to establish a dose of DTX401 that achieves symptom-free euglycemia (glucose ≥ 54 mg/dL [≥ 3.0 mmol/L]) in a setting of a controlled fasting challenge to allow further clinical development.

DTX401 will be administered as a single peripheral IV infusion. The following doses (per kilogram of body weight) may be evaluated using a CRM to estimate the MTD of DTX401:

- **Dose 1**: 2.0×10^{12} GC/kg
- **Dose 2**: 6.0×10^{12} GC/kg
- **Dose 3**: 1.0×10^{13} GC/kg

Eligible subjects may be enrolled into 1 of the following cohorts of 3 subjects each and receive a single IV infusion of DTX401.

- **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

A cohort may be expanded to include additional subjects to confirm the findings for the cohort.

Subjects in Cohorts 1 and 2 were dosed at a minimum of 2 weeks (14 days) apart. Subjects in subsequent cohorts will be dosed at a minimum of 1 week (7 days) apart.

For Cohorts 1 and 2, there was a minimum of 12 weeks (84 days) between dosing of the last subject in a dosing cohort and the first subject in the next dosing cohort. After the third subject in each cohort reached the 12-week time point, the CRM (Section 10.2.1) proposed a dose for the next cohort using the collected data from the previous cohort. The decision to proceed was made after the DMC evaluated at least 12 weeks of safety data for all subjects in the dosing cohort, as outlined in the DMC charter (Section 9.3). There were no intracohort dose escalations.

After reviewing Week 12 data from all subjects in Cohort 1, the DMC concluded that it was safe to enroll 3 additional subjects into Cohort 2 at Dose 2 (6.0×10^{12} GC/kg). After reviewing Week 12 data from all subjects in Cohort 2, the DMC concluded that it was safe to enroll 3 additional subjects into Cohort 3 at Dose 2 (6.0×10^{12} GC/kg) with an optimized reactive steroid regimen. An optimized reactive steroid regimen is expected to manage the elevations in liver aminotransferase levels observed in Cohorts 1 and 2 following DTX401 administration. If the optimized reactive steroid regimen does not sufficiently manage elevations in liver aminotransferase levels in Cohort 3, then Cohort 4 will be enrolled. Enrollment into Cohort 4 may begin following completion of enrollment into Cohort 3.

Subjects in Cohorts 1, 2, and 3 will receive reactive oral steroid treatment for possible vector-induced hepatitis if liver aminotransferase levels increase following treatment with DTX401. The Investigator, in conjunction with the Ultragenyx medical lead, will consider starting oral steroid treatment for possible vector-induced hepatitis if a subject's ALT levels increase from the subject's baseline or recently drawn levels, and are considered by the Investigator to be possibly related to treatment with DTX401 (Section 8.2.6.2.1). For Cohort 3, the reactive steroid regimen was modified to include a higher prednisone starting dose of 60 mg/day vs 40 mg/day.

Subjects in Cohort 4 will receive a prophylactic oral steroid regimen to prevent possible vector-induced hepatitis (Section 8.2.6.2.2). The Investigator may consider additional assessments or medical care, such as hospitalization or daily clinic visits, during steroid administration if, in the Investigator's medical judgment, these measures would provide additional safety benefits.

The controlled fasting challenge was also modified following DMC review of Week 12 data from subjects in Cohort 2. To minimize a potential insulin spike that could result in abrupt hypoglycemia and normalize baseline glucose levels, the recommended target carbohydrate range of the prefasting challenge dinner meal was decreased from 20 g to 30 g to 15 g to 20 g, and the prefasting challenge cornstarch dose was decreased from 35 g to 5 g.

However, further analysis and review of fasting challenge data after changing the prefasting cornstarch dose to 5g showed significantly lower fasting times in cohorts 2 (W52 and W78) and 3 (W24, W32 and W52). In most instances, low post-prandial levels of blood glucose associates, persistence of high circulating insulin levels, and slow cortisol response to hypoglycemia make it challenging to interpret these results. Available CGM recordings have shown an absence of nocturnal hypoglycemia in these subjects despite an overall reduced frequency and total amount of cornstarch. The reason that several subjects can now sleep through the night at home without experiencing hypoglycemia in the absence of cornstarch consumption, but have shorter time to hypoglycemia during the inpatient fasting challenge is unclear. It could be attributed to the artificial threshold of 60 mg/dL for stopping the fasting challenge. This threshold may not allow adequate glucose release to be induced in subjects with higher insulin and lower cortisol levels. In the home setting, subjects clearly do better as their glucose release seems to be better induced, thereby preventing their glucose levels from falling to dangerous levels.

With Protocol Amendment 6, the dinner meal will be personalized for each subject, and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers

that is as close as possible to the subject's most current dinner prescription but not higher than the carbohydrate content of the dinner consumed at their baseline fasting challenge. The prefasting cornstarch dose and time of consumption will be per the respective subject's most recent cornstarch prescription and daily regimen at home. In addition, the threshold for stopping the test was lowered to 54 mg/dL (3 mmol/L) or when the subjects present signs and symptoms of hypoglycemia. Justification of the new threshold is based on the fact that signs and symptoms of hypoglycemia associated with an adrenergic reaction and cerebral glucopenia and most physiological hormonal and metabolic responses to hypoglycemia may not occur in GSDIa subjects until they reach these levels of blood glucose values. CGM recording during the fasting test will provide continuous glucose measurement data that will allow Investigators to closely monitor subjects when they reach the lower range of blood glucose (ie, below 60 mg/dL) (Section 8.1.1).

Study enrollment will be stopped and the DMC and regulators will be notified if, at any time during the study, any of the safety stopping criteria are met (Section 3.2.4).

Subjects will be followed for 52 weeks following DTX401 administration. After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment into a 4-year extension study to evaluate the long-term (a total of 5 years) safety and efficacy of DTX401.

3.2. Overall Study Duration and Follow-Up

The study is anticipated to enroll approximately 12 subjects at up to 12 study sites globally. The duration of the study for each subject is defined as the date the subject provides written informed consent through the Week 52 visit. Subjects will be in the study for approximately 60 weeks (including the Screening Period).

Subjects will be asked to complete up to 4 inpatient study site visits (each approximately 24 to 48 hours in length) and 23 outpatient or home study visits (each approximately 1.5 to 2 hours in length). Outpatient or home study visits may be performed at a second participating study site other than the dosing site. The schedule of study visits and the assessments and procedures to be performed at each study visit are listed in the Schedule of Events (Table 6).

A high-level overview of the study is provided in Figure 2.

Figure 2: Study Overview

Screening Period (Day −56 to Day −1)

- Obtain informed consent
  - Collect samples (blood) for *G6PC* genotyping and AAV8 neutralizing antibody testing
- Determine subject eligibility
- Perform ECG and liver ultrasound
- Collect samples (blood and urine) for clinical and specialty laboratory assessments
- Record the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake during scheduled study visits and, if possible, on a weekly basis through the Week 52 visit or early withdrawal
- Assess symptomatic hypoglycemic events
- Provide copies of the GSDIa Morning Diary and GSDIa Evening Diary to subject
- Provide CGM device to subject

Baseline (Day 0 through Day 2)

Inpatient stay (approximately 48 hours)

- Confirm subject eligibility
- Collect samples (blood and urine) for clinical and specialty laboratory assessments
- Collect samples (saliva, urine, and stool) for vector shedding analysis (Day 0)
- Perform ECG
- Record the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake (Day 0)
- Assess symptomatic hypoglycemic events
- [redacted]
- Subject will complete GSDIa Morning Diary and GSDIa Evening Diary for 7 days leading up to and including Day 0
- Complete controlled fasting challenge and 24-hour urine collection (Day 0)
- Perform [redacted] (after the controlled fasting challenge is complete)
- For Cohort 4, initiate prophylactic steroid regimen after completion of the controlled fasting challenge and before DTX401 administration (Day 1)
- Administer DTX401 (Day 1)
- Collect sample (blood) for vector genome determination (Day 1 [predose] and Day 2 [postdose])
- Discharge subject (24 hours after DTX401 administration) with prednisone per the reactive (Cohort 3) or prophylactic (Cohort 4) steroid regimen

Enrollment Period

- Subjects in Cohorts 1 and 2 were dosed at a minimum of 2 weeks (14 days) apart. Subjects in subsequent cohorts will be dosed at a minimum of 1 week (7 days) apart.

- For Cohorts 1 and 2, there was a minimum of 12 weeks (84 days) between dosing of the last subject in a dosing cohort and the first subject in the next dosing cohort. The decision to proceed to the proposed next dose cohort was made after the DMC reviewed safety data for all subjects in a cohort after all subjects in the cohort completed Week 12.
- Following DMC evaluation of 12-week data from Cohorts 1 and 2, subjects may be enrolled into Cohort 3 with an optimized reactive steroid regimen. If the optimized reactive steroid regimen does not sufficiently manage elevations in liver aminotransferase levels in Cohort 3, then Cohort 4 will be enrolled. Subjects in Cohort 4 will receive a prophylactic steroid regimen. Enrollment into Cohort 4 may begin following completion of enrollment into Cohort 3.

Follow-up Period: Inpatient Visits (Weeks 12 and 24)

Inpatient stay (approximately 24 hours)

- Perform targeted physical examination
- Collect samples (blood and urine) for clinical and specialty laboratory assessments
- Collect samples (saliva, urine, and stool) for vector shedding analysis
- Collect sample (blood) for vector genome determination
- Record the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake during scheduled study visits and, if possible, on a weekly basis through the Week 52 visit or early withdrawal
- If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, review the subject's worksheet and provide a new worksheet to the subject
- Assess symptomatic hypoglycemic events
- [redacted]
- Subject will complete GSDIa Morning Diary and GSDIa Evening Diary for 7 days leading up to and including each inpatient visit
- Subject will complete a brief telephone interview regarding their experience completing [redacted] (Week 24 only)
- Complete controlled fasting challenge and 24-hour urine collection
- Perform [redacted] (after the controlled fasting challenge is complete)

Follow-up Period: Outpatient Study Site Visits (Weeks 4, 6, and 36)

- Perform targeted physical examination
- Collect samples (blood and urine) for clinical and specialty laboratory assessments
- Collect samples (saliva, urine, and stool) for vector shedding analysis
- Collect sample (blood) for vector genome determination
- Record the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake during scheduled study visits and, if possible, on a weekly basis through the Week 52 visit or early withdrawal
- If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, review the subject's worksheet and provide a new worksheet to the subject
- Assess symptomatic hypoglycemic events

Follow-up Period: Outpatient Study Site or Home Visits
• Biological samples will be collected at a minimum of every 3 to 4 days through Week 12, or longer if clinically indicated, either at the study site or by a home healthcare nurse (if arranged by the Investigator). Outpatient or home study visits may be performed at a second participating study site other than the dosing site.
End of Study (Week 52)/Early Withdrawal
Inpatient stay (approximately 24 hours) • Collect samples (blood and urine) for clinical and specialty laboratory assessments • Collect samples (saliva, urine, and stool) for vector shedding analysis • Collect sample (blood) for vector genome determination • Perform ECG • Record the subject's daily prescribed diet, daily diet intake, daily prescribed cornstarch (or equivalent), and daily cornstarch (or equivalent) intake • If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, review the subject's worksheet and provide a new worksheet to the subject • Assess symptomatic hypoglycemic events • [redacted] • Subject will complete GSDIa Morning Diary and GSDIa Evening Diary for 7 days leading up to and including Week 52 visit • Subject will complete a brief telephone interview regarding their experience in the study and completing [redacted] • Complete controlled fasting challenge and 24-hour urine collection • Perform [redacted] (after the controlled fasting challenge is complete) • Offer subject enrollment into the long-term (4-year) extension study • Discharge subject

Abbreviations: AAV8 = adeno-associated virus serotype 8; CGM = continuous glucose monitoring; DMC = data monitoring committee; ECG = electrocardiogram; *G6PC* = glucose-6-phosphatase (gene); GSDIa = glycogen storage disease type Ia; [redacted].

3.2.1. Screening Period

After a subject has provided written informed consent and within the 56 days prior to Day 0, the Investigator or other qualified study personnel will determine if the subject is eligible for the study. This will be accomplished by reviewing the inclusion and exclusion criteria (Section 4) and completing all of the screening assessments outlined in the Schedule of Events (Table 6).

Screening assessments may be performed on more than 1 day; all assessments must be completed and results available and reviewed within the 56-day Screening Period prior to Day 0. It is recommended that blood samples for AAV8 neutralizing antibody testing (Section 8.2.6.6) and *G6PC* genotyping (Section 8.3) be collected at the time written informed consent is provided.

Subjects with screening assessment results that do not fulfill eligibility requirements may have those assessments repeated if the study team determines that the underlying issue may resolve or reverse during the Screening Period (eg, Screening laboratory assessments, such as liver function tests and triglyceride levels). Only the screening assessments that do not meet eligibility requirements need to be repeated, but any or all screening procedures may be repeated at the Investigator's discretion.

Subjects who do not meet eligibility requirements within the Screening Period are considered screen failures. Subjects who are screen failures may be rescreened once during the study. In this case, only AAV8 neutralizing antibody testing (Section 8.2.6.6) and the screening assessments that did not meet eligibility requirements need to be repeated, but any or all screening procedures may be repeated at the Investigator's discretion.

3.2.2. Baseline Period

Subjects will be admitted to the study site or hospital on Day 0 and will be discharged approximately 24 hours after administration of DTX401 (on Day 2). Each subject will remain on his or her prescribed diet for the duration of the inpatient stay.

A blood sample for measurement of lipid levels will be collected on the morning of hospital admission. The sample should be collected at least 2 to 4 hours after the subject's last meal.

3.2.2.1. Baseline Visit – Day 0

The assessments and procedures to be performed during the Baseline (Day 0) visit are listed in the Schedule of Events (Table 6). [redacted] will be performed after the controlled fasting challenge is complete to avoid having to replace the sensor prior to the fasting challenge. (Section 8.1.4).

Subjects will participate in a controlled fasting challenge. The Investigator or delegated sub-investigator will review the results of all laboratory assessments performed on the first day of the inpatient visit, including cortisol. Subjects should wear their CGM device throughout the fasting challenge, and should not change the sensor prior to the assessment. Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner dietary prescription. The content of the dinner and quantities consumed will be recorded.

After dinner, subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription at approximately the same time that they typically take it, but no later than 3 hours post dinner. The time of ingestion of prefasting cornstarch and the amount consumed will be recorded. After the cornstarch is ingested, the controlled fasting challenge will begin, and the start time will be recorded accordingly. If subjects do not receive cornstarch overnight, the fasting test will begin after they complete their dinner. Subjects will be instructed to minimize activity after they finish eating dinner until the end of the fasting challenge.

During the fast, subjects may not ingest any food or drink other than water. The controlled fasting challenge will end when the subject's glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or subjects experience signs and symptoms of hypoglycemia, or the fast reaches 15 hours without hypoglycemia, whichever occurs first. The stop time of the controlled fasting challenge will be recorded. At the end of the controlled fasting challenge, the subject's hypoglycemia should be treated per the institution's standard procedure, which may include providing the subject with a meal, cornstarch, or IV glucose, if medically indicated.

Blood samples for measurement of cortisol, fatty acid, glucagon, insulin, C-peptide, growth hormone, insulin-like growth factor-binding protein 1 (IGFBP1), adrenocorticotropic hormone (ACTH), alanine and ketone levels will be collected at the beginning and end of the fasting challenge, or more frequently at the Investigator's discretion. A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Blood samples for STAT analysis of glucose and lactate will be collected per the schedule of events. Capillary glucose will also be assessed.

Urine will be collected over 24 hours for the determination of total protein, microalbumin, and creatinine. The collection of urine can overlap with the controlled fasting challenge. A [redacted] will be performed after the controlled fasting challenge is complete.

For subjects enrolled in Cohort 4, the Investigator will initiate a prophylactic steroid regimen after completion of the controlled fasting challenge and before DTX401 administration (Section 8.2.6.2.2).

3.2.2.2. Baseline Visit – Day 1

The assessments and procedures to be performed on Day 1 are listed in the Schedule of Events (Table 6).

Following completion of the Day 0 assessments (ie, controlled fasting challenge and 24-hour urine collection), subjects will receive a single, peripheral IV infusion of DTX401.
Safety (vital sign measurements [Section 8.2.1], clinical laboratory assessments [Section 8.2.6], and AEs and SAEs [Section 9.1]) will be monitored over 24 hours following infusion of DTX401 (Table 6). Any AEs that occur during this 24-hour observation period will be treated with appropriate supportive and medical care deemed necessary for the well-being of the subject.

Subjects will be discharged after a 24-hour observation period. Subjects in Cohort 3 will be discharged with prednisone to allow rapid treatment of possible vector-induced hepatitis if it occurs following treatment with DTX401 (Section 8.2.6.2.1). Subjects in Cohort 4 will be discharged with prednisone per the prophylactic steroid regimen (Section 8.2.6.2.2).

3.2.3. Follow-up Period

Subjects will be asked to visit the study site at a minimum of every 3 to 4 days through Week 12, or longer if clinically indicated (Table 6). Following the Week 12 visit, subjects will visit the

study site approximately once every 12 weeks through Week 36 and at Week 52 or their early withdrawal from the study (Table 6).

3.2.3.1. Outpatient Study Site or Home Visits

Subjects will be asked to provide clinical laboratory samples at a minimum of every 3 to 4 days through Week 12 of the study, or longer if clinically indicated (Table 6). Subjects may have the option of having these samples collected at their homes by clinically trained and qualified personnel (if arranged by the Investigator), unless there is a scheduled study site visit that the subject must attend in person (Table 6).

During these visits, a blood sample will be collected for determination of clinical chemistry (including liver function tests) and sent to the central laboratory. A second blood sample will be collected for liver function tests and sent to the local laboratory (STAT sample; Section 8.2.6.2). Saliva, urine, and stool samples will also be collected during these visits for assessment of vector shedding until at least 3 consecutive negative results are obtained from each sample matrix (Section 8.2.6.10). A blood sample will be collected for determination of cell-mediated immune response to AAV8 and G6Pase testing approximately weekly (Section 8.2.6.7).

3.2.3.2. Outpatient Visits

Subjects will visit the study site on an outpatient basis at Weeks 4, 6, and 36 for efficacy and safety assessments as outlined in the Schedule of Events (Table 6).

3.2.3.3. Inpatient Visits

Subjects will be admitted to the study site or hospital at Weeks 12, 24, and 52 for an [redacted] (Section 8.1.4), the controlled fasting challenge (Section 8.1.1), and 24-hour urine collection (Section 8.2.6.5). Each inpatient visit will last approximately 24 hours. Each subject will remain on his or her prescribed diet for the duration of each inpatient stay. The assessments and procedures to be performed at each visit are listed in the Schedule of Events (Table 6). The [redacted] will be performed on the day after the controlled fasting challenge to avoid having to replace the sensor prior to the fasting challenge.

A blood sample for measurement of lipid levels will be collected on the morning of hospital admission at approximately the same time as collected on Day 0. The sample should be collected at least 2 to 4 hours after the subject's last meal.

Subjects will participate in a controlled fasting challenge (Section 8.1.1). The Investigator or delegated sub-investigator will review the results of all laboratory assessments performed on the first day of the inpatient visit, including the latest cortisol values. Subjects should wear their CGM device throughout the fasting challenge, and should not change the sensor prior to the assessment. Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner dietary prescription. The content of the dinner and quantities consumed will be recorded.

After dinner, subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription at approximately the same time that they typically take it, but no later than 3 hours post dinner. The time of ingestion of prefasting cornstarch and the amount consumed will be recorded. After the cornstarch is ingested, the controlled fasting challenge will begin, and the start time will be recorded accordingly. If subjects do not receive cornstarch overnight, the fasting test will begin after they complete their dinner. Subjects will be instructed to minimize activity after they finish eating dinner until the end of the fasting challenge.

During the fast, subjects may not ingest any food or drink other than water. The controlled fasting challenge will end when the subject's glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or when the subjects experience signs and symptoms of hypoglycemia, or when the fast reaches 15 hours without hypoglycemia, whichever occurs first. The stop time of the controlled fasting challenge will be recorded.

At the end of the controlled fasting challenge, the subject's hypoglycemia should be treated per the institution's standard procedure, which may include providing the subject with a meal, cornstarch, or IV glucose, if medically indicated.

Blood samples for measurement of cortisol, fatty acid, glucagon, insulin, C-peptide, growth hormone, IGFBP1, ACTH, alanine and ketone levels will be collected at the beginning and end of the fasting challenge, or more frequently at the Investigator's discretion. A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Blood samples for STAT analysis of glucose and lactate will be collected per the schedule of events. Capillary glucose will also be assessed. Urine will be collected over 24 hours (Section 8.2.6.5) for the determination of total protein, microalbumin, and creatinine. The collection of urine can overlap with the controlled fasting challenge. Subjects will be discharged following the completion of the 24-hour urine collection and the [redacted].

3.2.4. Safety Stopping Criteria

Enrollment will be stopped and the DMC and regulators will be notified if, at any time during the study, any of the events listed below occur following administration of DTX401:

- Death of a subject
- An event with an intensity ≥ Grade 3 (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) develops
- Occurrence of a hepatic malignancy

If a stopping rule is met, enrollment will be paused and the DMC will meet to review available data. If a decision is made to resume enrollment, this decision will be communicated to and, if required, approved by regulatory authorities according to country requirements.

An event that meets the above criteria will be reported immediately to the Sponsor once the study site has become aware (within 24 hours). SAEs will be reported as outlined in

Section 9.1.2.2. For AEs and SAEs, the appropriate pages of the electronic case report form (eCRF) must be completed. If a stopping criterion is met and study enrollment is suspended, all subjects who have been enrolled will remain in the study and will continue to be monitored through their completion or withdrawal from the study.

3.2.5. End of Study

Subjects who complete all visits up to and including the Week 52 visit (Section 3.2.3.3) will have completed the study. Subjects who discontinue before the Week 52 visit will be asked to return for an Early Withdrawal visit, during which all safety assessments should be performed (Table 6). Subjects with any ongoing AEs at this visit will continue to be monitored, as outlined in Section 9.1.5. After completion of the Week 52 visit or early withdrawal, subjects will be offered enrollment into this extension study in accordance with regulatory authority regulations and ICH GCP.

3.3. Changes to the Protocol due to COVID-19

Changes to the protocol or Investigational Plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants and/or study staff may be implemented without IRB/EC approval or before filing an amendment to the competent authority but are required to be reported afterward. Investigators should contact Ultragenyx or Designee to determine an appropriate course of action, which may include but is not limited to remote visits, home health visits, and out of window visits or assessments. Any changes to the protocol or investigational plan must be documented. The Investigator will work with Ultragenyx or Designee and IRB/EC to prioritize reporting of protocol deviations that impact safety of trial participants.

4. SUBJECT SELECTION

Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1. Inclusion Criteria

Each subject must meet all of the following criteria at Screening to be enrolled in this study:

1. Willing and able to provide written informed consent.
2. Males and females ≥ 18 years of age.
3. Documented GSDIa with confirmation by molecular testing.
4. Documented history of ≥ 1 hypoglycemic event with glucose < 60 mg/dL (< 3.33 mmol/L).
5. Subject's GSDIa disease is stable as evidenced by no hospitalization for severe hypoglycemia during the 4-week period preceding the Screening Visit.
6. Hematology and coagulation panel results are within the normal range or, if outside the normal range, are deemed not clinically significant in the opinion of the Investigator.
7. No known allergic reaction to any component of DTX401.
8. Willing and able to comply with study procedures and requirements, including periodic inpatient hospitalization, frequent blood collections, and 24-hour urine collection.
9. Males and females of childbearing potential must be willing to use effective contraception at the time of administration of DTX401 and for 52 weeks following administration of DTX401 to prevent the potential transmission of the AAV vector (Section 9.2.1).

4.2. Exclusion Criteria

Subjects who meet any of the following criteria at Screening will be excluded from the study:

1. Screening or Baseline (Day 0) glucose level < 60 mg/dL (< 3.33 mmol/L); subjects may be rescreened after glucose is controlled and stable, at the discretion of the Investigator.
2. Liver transplant, including hepatocyte cell therapy/transplant.
3. Presence of liver adenoma > 5 cm in size.
4. Presence of liver adenoma > 3 cm and ≤ 5 cm in size that has a documented annual growth rate of ≥ 0.5 cm per year.

5. Significant hepatic inflammation or cirrhosis as evidenced by imaging or any of the following laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase > the upper limit of normal (ULN), total bilirubin > 1.5 × ULN, or alkaline phosphatase > 2.5 × ULN. Liver function tests may be repeated during the Screening Period at the Investigator's discretion.

6. Serum creatinine > 2.0 mg/dL.

7. Triglycerides ≥ 1000 mg/dL at the time of the Screening Visit.

8. Presence of active, or history of treatment for, hepatitis B virus or hepatitis C virus infection.

9. History of human immunodeficiency virus infection AND any of the following: CD4+ cell count < 350 cells/mm^3, change in antiretroviral therapy regimen within 6 months prior to Day 0, or viral load > 200 copies/mL, on 2 separate occasions, as measured by polymerase chain reaction.

10. History of a malignancy for which the subject has received treatment in the past 2 years except for prostate cancer treated with watchful waiting or surgically removed nonmelanoma skin cancer.

11. Active infection (viral or bacterial).

12. Anti-AAV8 neutralizing antibody titer ≥ 1:5.

13. Participation (current or previous) in another gene transfer study.

14. Participation in another investigational product study within 3 months of Screening.

15. Has a positive serum pregnancy test at Screening (females of childbearing potential only), a positive urine pregnancy test at Baseline (Day 0; females of childbearing potential only), or is nursing.

16. Has any other significant medical condition that the Investigator feels would be a risk to the subject or would impede the study.

5. SCREENING AND DOSING PROCEDURES

5.1. Subject Screening

All potential subjects must sign an informed consent form (ICF) before any study procedures or assessments are performed or initiated (Section 11.3). Subjects will have the opportunity to have any questions answered before signing the ICF. All questions raised by the subject must be addressed before the Investigator also signs the ICF. A copy of the signed ICF will be given to the subject.

Rescreening is allowed as described in Section 3.2.1. Study sites will maintain documentation of all potential subjects screened for inclusion in the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

5.2. Subject Dosing

This is an open-label study; subjects will be assigned to treatment using an interactive web response system. Three subjects will be enrolled in each cohort as described in Section 3.1.

6. STUDY TREATMENT

6.1. Identity of Study Product

6.1.1. Description of DTX401

DTX401 is a nonreplicating, recombinant AAV8 vector that contains a codon-optimized, wild-type human *G6PC* coding sequence. DTX401 demonstrates thermal stability, which is a general property of AAV and parvoviruses. DTX401 is supplied as a slightly hyperosmotic buffered formulation solution of approximately 400 milliosmole at pH 8.0. DTX401 is a homogeneous, monodisperse solution that is clear and colorless without visible particulates.

6.1.2. Components Used for Manufacturing

[redacted] For additional information, please refer to the DTX401 Investigator's Brochure.

6.2. Management of Clinical Supplies

The study site will be provided with supplies required for infusion of DTX401.

6.2.1. Packaging and Labeling

Each vial of study product provided to study sites will contain approximately 1 mL of DTX401 frozen in 2 mL sterile glass vials with a primary label on the vial. Study product will have secondary packaging with a secondary label. The primary label meets all requirements for blister and small packaging units. The secondary label will contain required text for all countries participating in the study and will include a unique identifier. Secondary labeling will appear in the appropriate language for the country supplied.

6.2.2. Storage of DTX401

DTX401 must be stored in a secure freezer at a controlled temperature at or below −60°C. The study site is to maintain a daily log documenting the temperature.

6.2.3. Study Product Accountability

The Investigator or designated study site staff will maintain accurate records of receipt of all study product, including dates of receipt. In addition, accurate records will be kept regarding when and how much study product is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, all study product will be reconciled and retained or destroyed according to instructions provided by the Sponsor.

6.2.4. Transmission of Infectious Agents

Recombinant AAV vectors are nonreplicative and are not expected to pose a risk of transmission. However, all sexually active subjects must use approved contraception from the time of DTX401 dosing and for 52 weeks following administration (Section 4.1). All subjects enrolled in the study should be encouraged to discuss the use of approved contraception with his or her partner in order to prevent possible transmission of vector via seminal or vaginal fluid. The study product and post treatment study samples should be handled using standard universal precautions.

6.3. Treatment Schedule and Administration

6.3.1. Administration of DTX401

Subjects will receive a single peripheral IV infusion of DTX401 on Day 1, administered by qualified study personnel, as designated by the Investigator (Table 6). The dose will be determined by the cohort and candidate dose (Section 3.1).

The dose of DTX401 to be administered will be calculated using the subject's weight recorded at Screening. The subject's weight will be verified on Day 0, prior to administration of DTX401, to ensure that their current weight is within 10% of their screening weight (Section 8.2.1). Any subject weighing > 100 kg (> 220 lb) will be dosed as if his or her weight is 100 kg. Prior to infusion, all infusion bag labels will be checked by the study site pharmacist and a minimum of 2 medical personnel charged with administration of DTX401.

The study site must be equipped with emergency resuscitation capabilities. On Day 1, an IV catheter will be inserted into a peripheral vein and flushed with saline.

Detailed instructions for dose preparation and subsequent infusion of DTX401 are provided in the pharmacy manual.

6.3.2. Treatment Compliance

DTX401 will be administered at the study site via a single IV infusion administered by qualified personnel. The dose, start time, stop time, and volume of infusion will be recorded in the subject's eCRF.

6.4. Prior and Concomitant Medications, Therapies, and Procedures

Relevant prior and concomitant medications, therapies, and procedures will be recorded in the subject's eCRF. The minimum requirement for medications is to record the drug name, the dates of administration, and the reason for use. This includes all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medication use will also be recorded in the subject's eCRF. The minimum requirement for therapies and procedures is to record the name and date of the therapy or procedure and the reason it was performed.

6.4.1. Permitted Medications

The use of permitted medications (including drug name, dates of administration, dosage, reason for use) will be recorded on the appropriate page of the eCRF.

The subject will be instructed to discuss all new medications, including medications to alleviate complications associated with GSDIa and herbal supplements, with the Investigator at each study visit.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given. It is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

6.4.2. Prohibited Medications

Use of another investigational product is prohibited from Screening through Week 52.

7. WITHDRAWAL OF SUBJECTS FROM THE STUDY

7.1. Study Withdrawal

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Any subject who withdraws consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of request.

The Investigator must record the reason for withdrawal on the appropriate page of the eCRF. The reason for withdrawal may include the following:

- Withdrawal of consent
- Administrative decision by the Investigator or the Sponsor
- Ineligibility
- Significant protocol deviation
- Subject noncompliance
- Adverse event

If a subject is withdrawn due to an AE, the Investigator will arrange for the subject to have follow-up visits until the AE has resolved or stabilized (Section 9.1.5).

If a subject requests or decides to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal, and an early withdrawal visit will be requested.

7.2. Subject Replacement

If a subject withdraws from the study after receiving DTX401, the subject will not be replaced. Subjects who withdraw from the study after signing the ICF, but before receiving DTX401, will be replaced. The replacement subject will be sequentially assigned to treatment with a new subject identification number.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Efficacy Assessments

Planned time points for all efficacy measurements in the study are listed in Table 6.

8.1.1. Symptom-Free Euglycemia (Controlled Fasting Challenge)

The subject's ability to maintain symptom-free euglycemia during a controlled fasting challenge will be assessed at time points specified in the Schedule of Events. However, if clinically indicated, the controlled fasting challenge can also be performed at an unscheduled visit.

The controlled fasting challenge requires a 24-hour inpatient stay in a hospital or research facility and will be performed after all other study visit assessments (except [redacted]) have been completed and the required laboratory assessments (as specified below) have been reviewed by the Investigator (or a subinvestigator assigned to review results and make clinical decisions per the site delegation log). Subjects should wear their CGM device throughout the fasting challenge, and should not change the sensor prior to the assessment.

If a subject is suspected to have HPA axis impairment (eg, due to prolonged steroid treatment; may be confirmed by morning cortisol or stimulation tests), the fasting challenge may have to be rescheduled to a later date in order to ensure subject safety and provide interpretable results.

Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject, and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject’s most current dinner prescription, but not higher in carbohydrate content than the dinner consumed at their baseline fasting challenge. The start and stop time of the dinner meal and its full dietary composition including amount of carbohydrates consumed will be recorded. After dinner, subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription, at approximately the same time that they typically take it, but no later than 3 hours post dinner. The amount of cornstarch administered should not be higher than that consumed by the subject at the baseline fasting challenge. The time of ingestion of prefasting cornstarch and the amount consumed will be recorded. After the cornstarch is ingested, the controlled fasting challenge will begin, and the start time will be recorded accordingly. If a subject does not receive cornstarch before going to bed at the time of the CFC, the fasting challenge will start after they complete their dinner. Subjects will be instructed to minimize activity after they finish eating dinner until the end of the controlled fasting challenge.

During the fast, subjects may not ingest any food or drink other than water. The controlled fasting challenge will end when the subject’s glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or when the subjects experience signs and symptoms of hypoglycemia, or when the fast reaches 15 hours without hypoglycemia, whichever occurs first. The stop time of the controlled fasting challenge will be recorded. At the end of the controlled fasting challenge, the subject’s hypoglycemia should be treated per the institution’s standard procedure, which may include providing the subject with a meal, cornstarch, or IV glucose, if medically indicated.

In cases where the controlled fasting challenge is terminated prematurely before the subject reaches a glucose level of < 54mg/dL or without the subject experiencing signs and symptoms of hypoglycemia, or due to any deviation in the fasting challenge protocol, an ad hoc fasting challenge may be scheduled within 6 weeks from the scheduled fasting challenge.

Laboratory sample collection before and during the controlled fasting challenge

On the morning of inpatient visit for the controlled fasting challenge, after vital signs and other non-interventional assessments have been performed, samples will be collected for standard clinical chemistry (including lipid levels), hematology, coagulation panel, and urinalysis. These samples should be collected at least 2 to 4 hours after the subject's last meal prior to admission and sent to the central lab. A sample for STAT AST and ALT level analysis will also be collected at this time and sent to the local laboratory; the Investigator or delegated subinvestigator should review the results before starting the controlled fasting challenge.

All subjects should have a morning cortisol and ACTH measurement prior to their baseline fasting challenge. Cortisol and ACTH results should be reviewed by the Investigator or delegate before starting the fasting challenge. Abnormal morning cortisol results might require postponing the fasting challenge until further HPA axis testing is performed.

For subjects with suspected HPA axis dysfunction (eg, after prolonged steroid treatment) supplemental tests can be conducted (eg, stimulation tests) before deciding if it is safe to conduct the fasting challenge. In most cases, morning cortisol and supplemental tests will be conducted one week prior to the visit. It is also possible to perform these tests at the site on Day 1 of the visit under the conditions that all results will be available prior to the beginning of the CFC.

Total urine voided over the 24-hour period starting at the time of inpatient admission will be collected during the controlled fasting challenge.

Blood samples for measurement of cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine and ketone levels (3-hydroxy butyrate) will be collected at the beginning (ie, immediately after the post-dinner dose of cornstarch, or immediately after dinner for subjects who do not take a post-dinner dose of cornstarch) and end of the controlled fasting challenge, or more frequently at the Investigator's discretion. A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures.

Blood samples for STAT analysis of glucose and lactate will be collected through an indwelling catheter (central or peripheral) at the following time points:

- At the beginning of the fast (ie, immediately after the post-dinner dose of cornstarch, or immediately after dinner for subjects who do not take a post-dinner dose of cornstarch)
- Approximately every 60 minutes (± 5 minutes) until the glucose level decreases to ≤ 70 mg/dL (≤ 3.9 mmol/L)

- Approximately every 30 minutes (± 5 minutes) until the glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or when the subjects experience signs and symptoms of hypoglycemia, or when the fast reaches 15 hours without hypoglycemia, whichever occurs first

Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. To ensure the safety of the study subjects, results from these tests should be available within 30 minutes after the blood sample collection. Capillary glucose will be performed at the same time points as blood samples for STAT analysis of glucose and lactate. Results of the capillary glucose and readings from CGM at corresponding time points will be noted on a controlled fasting challenge results sheet.

8.1.2. Continuous Glucose Monitoring

Supplemental information on glucose level trends will be collected using a continuous glucose monitoring (CGM) device. The site will provide a CGM device to the subject during the Screening Period after determining that the subject is eligible for the study (Table 6). Subjects will be educated on the appropriate care and use of the CGM device and sensors, and instructed to wear the CGM device through the Week 52 visit or early withdrawal. Data from the subject's CGM device will be transferred to the Sponsor throughout the study, including a final data transfer at the end of the Week 52 visit or early withdrawal. Details regarding the care and use of the CGM device and sensors and data transfer to the Sponsor are provided in the Manual of Operations.

8.1.3. 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 (Table 6). Subjects should adhere to their prescribed overnight cornstarch diet. Morning glucose levels should be measured using the subject's own glucose monitoring device before taking their morning dose of cornstarch. The collection date, collection time, glucose level, and prior day's overnight cornstarch dose taken should be collected on the Morning Glucose Level monitoring worksheet provided by the site. Subjects will be instructed to bring the completed worksheets to each study visit. Data collected on the worksheet will be captured on the appropriate page of the eCRF.

8.1.4. [redacted]

[redacted]

[redacted]

8.1.5. [redacted]

Subjects will be asked to complete the following [redacted]:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

8.1.6. Endpoint Outcomes Interviews

Up to two 30-minute scripted telephone interviews will be conducted during the Week 24 and 52 study visits to better quantify the subject experience in the study. The interviews will be conducted by a third-party vendor, Endpoint Outcomes, specializing in the capture of caregiver and subject-reported data. Endpoint Outcome uses a script as an interview guide to serve as a basis for the discussion. The interview will be conducted by phone.

The subject has consented to the interview per the study's main ICF. However, prior to the start for the interview, Endpoint Outcomes will verbally ask for the subject's consent for the interview to be audio-recorded. With the subject's verbal consent, the interview will be audio-recorded, and the interviewer will proceed through a script. If the subject does not give permission for the session to be audio-recorded, the interview will not proceed. Subjects will be asked about their experience in the study. They may refuse to answer any question in the interview and may stop at any time.

Site staff will facilitate the phone call so that the subject's contact information remains anonymous. Personal information (including subject's name and telephone number) will remain anonymous and will not be provided to the Sponsor or Endpoint Outcomes. Subjects will be identified only by their study specific subject IDs.

All digital recordings will be stored by Endpoint Outcomes in a secure place where only Endpoints Outcome personnel directly related to this study will be able to access it. The audio interviews will be transcribed by a transcription company under contract and a confidentiality agreement, who will provide the written transcripts that will be further analyzed by Endpoint Outcomes. The transcription company is also contracted to ensure that transcripts will not contain any personal identifying information (eg, reference of first names) that may have been revealed during the interview process; personal identifying information will be removed and will not appear in the final transcript. Data from the interview will be shared with the Sponsor only after all identifying information has been removed.

8.2. Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Events (Table 6).

Safety will be assessed based on AEs, SAEs, vital sign measurements, complete and targeted physical examination findings, ECG results, documented 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.

8.2.1. Vital Sign Measurements

Vital sign measurements will be made at the time points specified in the Schedule of Events (Table 6). During the study, vital sign measurements are to be collected before any stimulating or anxiety-provoking procedures (eg, phlebotomy). Vital sign measurements will include heart rate, blood pressure (systolic and diastolic), and respiratory rate. Height (at the Screening visit only) and weight will also be recorded.

- On Day 0, weight will be measured to ensure that the weight is within 10% of the screening weight used to calculate the dose of DTX401. Subjects with a confirmed change in weight that is > 10% from Screening should be further evaluated to exclude the presence of an acute condition or illness. If a benign explanation for the weight

change is identified and documented, DTX401 can be given and dosed using the weight obtained on Day 0.

- Vital signs should be measured with the subject having rested for at least 5 minutes beforehand. It is preferred that the measurement be late with the subject rested, rather than on time with the subject not sufficiently rested. If the subject is not sufficiently rested, this needs to be stated in the source documents.

- On Day 1, vital signs will be measured at predose, approximately 5 minutes, and 0.5 (± 5 minutes), 1 (± 5 minutes), 4 and 8 hours (± 15 minutes) after the start of DTX401 infusion. Vital signs will also be measured approximately 22 hours (± 1 hour) after the start of infusion, prior to subject discharge.

- It is acceptable for heart rate to be captured from the 12-lead ECG (Section 8.2.3).

Vital sign measurements will be recorded on the appropriate page of the eCRF. The medical monitor should be notified of any clinically significant changes or abnormal value in vital sign measurements (Section 9.1.2). If, in the medical and scientific judgment of the Investigator, a clinically significant change or abnormal vital sign measurement is observed, it should be recorded as an AE or SAE, as defined in Section 9.1.2, on the appropriate pages of the eCRF.

8.2.2. Physical Examination

A complete or targeted physical examination will be performed at the time points specified in the Schedule of Events (Table 6).

A complete physical examination will include assessments of the head, eyes, ears, nose, and throat; skin; abdomen with documentation of liver and spleen size; and the endocrine, metabolic, neurological, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems.

A targeted physical examination will include assessment of the skin, the abdomen with documentation of liver and spleen size, and the respiratory, cardiovascular, and gastrointestinal systems.

Physical examination findings will be captured on the appropriate page of the eCRF.

8.2.3. Electrocardiograms

An ECG will be performed at the time points specified in the Schedule of Events (Table 6).

- A single 12-lead ECG will be obtained at Screening, on Day 0 (Baseline), predose on Day 1, and at Week 52, using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT intervals.

Twelve-lead ECGs should be measured with the subject having rested for at least 5 minutes beforehand. It is preferred that the measurement be late with the subject rested, rather than on time with the subject not sufficiently rested. If the subject is not sufficiently rested, this needs to

be stated in the source documents. Electrocardiogram results will be recorded on the appropriate page of the eCRF.

8.2.4. Liver Ultrasound

An ultrasound of the liver will be conducted during the Screening Period. The ultrasound will be conducted and assessed at the study site. Ultrasound results will be recorded on the appropriate page of the eCRF.

8.2.5. Hypoglycemic Events

At each visit, the study site will instruct subjects on proper home glucose monitoring, the signs and symptoms of hypoglycemia, and supplemental glucose treatment if needed.
During Screening, the study site will record the number of symptomatic hypoglycemic events that occurred during the previous 52 weeks in the eCRF. During each subsequent visit, the study site will record the number of symptomatic hypoglycemic events that occurred since the last visit in the eCRF (Table 6).

8.2.6. Clinical Laboratory Assessments

Laboratory tests, including ALT, will be closely monitored throughout the duration of the study. Investigators will receive flagged notification of any laboratory values that are outside of the normal range. Any abnormal laboratory test results (clinical chemistry [including liver function tests], hematology, coagulation panel, urinalysis, or other laboratory parameters), including those that worsen from baseline or are felt to be clinically significant in the medical and scientific judgment of the Investigator, are to be recorded as AEs or SAEs (Section 9.1.2).

However, any clinically significant safety assessments that are associated with GSDIa are **not** to be reported as AEs, **unless** they are judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with results that are significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

Samples of blood, urine, saliva, and stool will be collected for study assessments. Any samples remaining at the end of the study may be stored for up to 15 years and analyzed to better understand the effect of DTX401 on GSDIa or other metabolic deficiencies. The choice to allow retention and future analysis will be optional.

8.2.6.1. Clinical Laboratory Parameters

The clinical laboratory parameters to be measured are listed in Table 2. Samples are to be collected at the time points specified in the Schedule of Events (Table 6).

Table 2: 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
Clinical chemistry (other):[a]	Glucose, lactate
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)
Other:	HBV surface antigen,[b] HCV RNA,[b] HIV,[b] *G6PC* genotyping,[b] serum pregnancy,[b] cortisol, free fatty acids, glucagon, insulin, C-peptide, growth hormone, ACTH, IGFBP1, alanine, ketones, AAV8 neutralizing antibody, AAV8 binding antibody IgG, cell-mediated immune response to AAV8 and G6Pase, anti-G6Pase antibody, vector genome, vector shedding
Coagulation panel:	PT/INR, aPTT

Abbreviations: ACTH: Adrenocorticotropic hormone; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; AAV8 = adeno-associated virus serotype 8; G6Pase = glucose-6-phosphatase (protein); *G6PC* = glucose-6-phosphatase (gene); HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGFBP1 = insulin-like growth factor-binding protein 1; IgG = immunoglobulin G; PT/INR = prothrombin time/international normalized ratio.

[a] Samples collected during the controlled fasting challenge should be sent to the local laboratory (STAT samples) for analysis.

[b] To be performed at Screening only.

Samples for measurement of glucose and lactate levels collected during the controlled fasting challenge should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Details for the preparation and shipment of all other samples will be provided by the central or specialty laboratory. Reference ranges for all parameters will be provided to the study site by the central or specialty laboratory.

If additional nonprotocol-specified laboratory assessments are performed at the study site's local laboratory and result in a change in subject management or the results are considered clinically significant by the Investigator (eg, SAE or AE), the results must be captured and sent to the Sponsor along with other study data, as defined in Section 9.1.2.

A laboratory parameter may be repeated if there is any concern about the values obtained.

8.2.6.2. Elevation of Liver Function Tests

In clinical studies with AAV-mediated gene transfer, a transient increase in liver aminotransferases and a concurrent decline in transgene expression have been observed (Manno et al., 2006; Nathwani et al., 2011b; Nathwani et al., 2014). This has been hypothesized to be due to the activation of capsid-specific cytotoxic T lymphocytes and destruction of transduced liver cells (Mingozzi et al., 2007). However, in mice, T cells activated against AAV capsid were not able to target and eliminate transduced hepatocytes (Wang et al., 2007; Li et al., 2007a; Li et al.,

2007b; Siders et al., 2009) unless the transduced hepatocytes co-expressed the wild-type AAV capsid protein (Li et al., 2007a).

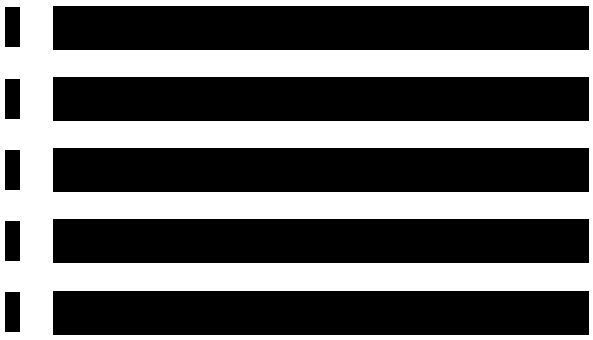
The inability to reproduce the observed effects in animal models has made it difficult to assess the validity of the hypothesis or to develop strategies to overcome or minimize aminotransferase elevations. Despite a lack of clear resolution that activation of cytotoxic T lymphocytes leads to a reduction in transgene expression from hepatocytes, appropriate precautions have been incorporated into this study. In addition to monitoring for capsid-specific and G6Pase-specific T-cell activation, subjects will receive oral steroid treatment for possible vector-induced hepatitis if liver function tests increase following treatment with DTX401 as outlined in Section 8.2.6.2.1. Subjects in Cohort 4 will receive prophylactic oral steroid treatment to prevent possible vector-induced hepatitis as outlined in Section 8.2.6.2.2.

Liver function tests will be assessed as part of clinical chemistry (Section 8.2.6.1) at the time points specified in the Schedule of Events (Table 6). Liver function tests will be assessed at the central laboratory and the local laboratory (STAT sample) at a minimum of every 3 to 4 days through Week 12, or longer if clinically indicated, to allow for a rapid detection of any liver aminotransferase elevations following administration of DTX401. An increase in liver function tests following treatment with DTX401 will be recorded as an AE or SAE, as defined in Section 9.1.2, on the appropriate pages of the eCRF if it is felt to be clinically significant in the medical and scientific judgment of the Investigator.

8.2.6.2.1. Reactive Steroid Treatment for Possible Vector-Induced Hepatitis

Subjects in Cohorts 1, 2, and 3 will receive reactive oral steroid treatment for possible vector-induced hepatitis if liver aminotransferase levels increase following treatment with DTX401. The Investigator, in conjunction with the Ultragenyx medical lead, will consider starting oral steroid treatment for possible vector-induced hepatitis if a subject's ALT levels increase from the subject's baseline or recently drawn levels, and are considered by the Investigator to be possibly related to treatment with DTX401. If repeat testing is deemed necessary, every effort should be made to repeat the testing within 24 hours from receipt of test results indicating elevated levels of ALT.

Based on available evidence, it is expected that vector-induced hepatitis will be self-limiting. Therefore, prednisone (or prednisolone) will be used to treat vector-induced hepatitis according to the American Association for the Study of Liver Disease guidelines, which have been modified for subjects with GSDIa so that the starting dose/duration is lower/shorter:



[redacted]

The Investigator, in conjunction with the Ultragenyx medical lead, may consider modifying this regimen if a subject's ALT levels do not normalize during the steroid taper. The Investigator should document the agreed upon steroid regimen in the subject's source documentation.

The use of prednisone will be recorded on the appropriate page of the eCRF.

8.2.6.2.2. Prophylactic Steroid Treatment for Vector-Induced Hepatitis

Subjects in Cohort 4 will receive prophylactic oral steroid treatment to prevent possible vector-induced hepatitis. Prophylactic oral steroid regimens have been used in AAV-mediated gene transfer clinical trials for other indications (eg, Clinicaltrials.gov identifiers: NCT03223194, NCT03306277).

Oral prednisone (or prednisolone) will be initiated on Day 1 following completion of the Day 0 controlled fasting challenge and before DTX401 administration as follows:

[redacted]

The Investigator, in conjunction with the Ultragenyx medical lead, may consider modifying this regimen if a subject's ALT levels do not normalize during the steroid taper.

Additional oral prednisolone/placebo may be administered after completion of the taper if a subject's alanine aminotransferase (ALT) levels increase from Baseline and/or above the ULN of recently drawn levels repeated one more time as soon as possible.

[redacted]

[redacted]

If, in the Investigator's medical judgment, the subject may not safely tolerate initiation of oral steroid treatment on Day 1, the steroid regimen may be modified based on discussion between the Investigator and the Ultragenyx medical lead. The Investigator should document the agreed upon steroid regimen in the subject's source documentation.

The Investigator may consider additional assessments or medical care, such as hospitalization or daily clinic visits, during steroid administration if, in the Investigator's medical judgment, these measures would provide additional safety benefits.

The use of prednisone will be recorded on the appropriate page of the eCRF.

Vaccination and Oral Prednisone Regimen

To comply with international and regional guidelines on vaccination, as well as slight variations in regional schedules, where feasible, subjects' vaccination schedules should be adjusted to accommodate prophylactic prednisone taper regimen administration prior to and following DTX301 infusion.

Live vaccines (such as MMR and varicella) are contraindicated for patients on a substantially immunosuppressive steroid dose (ie, ≥ 2 weeks of daily receipt of 20 mg of prednisone, or equivalent or 1 mg/kg/day in children under 20 kg) for more than 14 days. Thus, Investigators should time administration of live vaccines to at least 14 days prior to inception of the prednisone regimen, or after completion of the 8-week prednisone regimen.

Inactivated vaccines and seasonal influenza prophylaxis vaccination are not precluded to patients treated with immunosuppressive agents in accordance to international guidelines (Ezeanolue et al.; Rubin et al., 2014; Public Health England, 2020; ECDC, 2017; Public Health England, 2017). All inactivated vaccines can be administered safely to persons with altered immunocompetence, whether the vaccine is a killed whole-organism or a recombinant, subunit, split-virus, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine.

8.2.6.3. Lactate

At Baseline (Day 0) and Weeks 12, 24, and 52, lactate levels will be measured during the controlled fasting challenge (Section 8.1.1). A venous blood sample for lactate will be collected through an indwelling catheter (central or peripheral) as follows:

- At the beginning of the fasting challenge (ie, immediately after the post-dinner dose of cornstarch, or immediately after dinner for subjects who do not take a post-dinner dose of cornstarch)
- Approximately every 60 minutes (± 5 minutes) until the glucose level decreases to ≤ 70 mg/dL (≤ 3.9 mmol/L)

- Approximately every 30 minutes (± 5 minutes) until the glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or when the subjects experience signs and symptoms of hypoglycemia, or when the fast reaches 15 hours without hypoglycemia, whichever occurs first.

Lactate samples should be sent to the local laboratory (STAT sample) and results should be available within 30 minutes or less of blood sample collection. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures.

8.2.6.4. Other Controlled Fasting Challenge Laboratory Assessments

At Baseline (Day 0) and Weeks 12, 24, and 52, blood samples for measurement of cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine, and ketone levels will be collected at the beginning and end of the controlled fasting challenge, or more frequently at the Investigator's discretion (Section 8.1.1). A final sample for glucose, lactate, growth hormone, IGFBP1, ACTH, and cortisol measurement will be collected 30 minutes after the end of the controlled fasting challenge. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. Additionally, if possible, a blood sample for measurement of ACTH and cortisol levels will be collected approximately 1 week before the Week 12 visit. Details for the preparation and shipment of samples are included in the laboratory manual.

8.2.6.5. 24-Hour Urine Collection

The excretion of total protein, microalbumin, and creatinine in the urine will be determined over a 24-hour period. Timed 24-hour complete urine samples will be collected at Baseline (Day 0) and during inpatient visits as specified in the Schedule of Events (Table 6). Details for the preparation and shipment of samples are included in the laboratory manual.

8.2.6.6. Neutralizing Antibodies to Adeno-Associated Virus Serotype 8

A blood sample for determination of neutralizing antibodies to AAV8 will be collected at the time points specified in the Schedule of Events (Table 6) to monitor for a humoral immune response to AAV8. It is recommended that the Screening sample be collected at the time written informed consent is provided. The assay will be performed using a research method (cell-based assay).

8.2.6.7. Cell-Mediated Immune Response

The presence of T cells specific for AAV8 and G6Pase will be determined by an [redacted] A blood sample will be collected at the time points specified in the Schedule of Events (Table 6). Samples for the [redacted] assay will be collected approximately weekly through Week 12 and at Weeks 24, 36, and 52.

8.2.6.8. Adeno-Associated Virus Serotype 8 Binding Antibody Immunoglobulin G Assay

A blood sample for the AAV8 binding antibody IgG assay will be collected at the time points specified in the Schedule of Events (Table 6) to monitor for circulating anti-AAV8 antibodies. The assay will be performed using a research method [redacted]

8.2.6.9. Anti-Glucose-6-Phosphatase Antibody Assay

A blood sample for the anti-G6Pase antibody assay will be collected at the time points specified in the Schedule of Events (Table 6) to monitor for circulating anti-G6Pase antibodies. The assay will be performed using a research method.

8.2.6.10. Vector Shedding

Saliva, urine, and stool samples will be collected at the time points specified in the Schedule of Events (Table 6) to monitor for vector shedding. The presence of DTX401 will be determined by [redacted]. Subjects will be given an appropriate container to collect a stool sample at home. Saliva and urine samples will be collected at the study site for inpatient visits (Table 6). Subjects may have the option of having these samples collected at their homes by clinically trained and qualified personnel (if arranged by the Investigator), unless there is a scheduled study site visit that the subject must attend in person. Samples for vector shedding analysis will be collected until at least 3 consecutive negative results are obtained for each sample matrix.

8.2.6.11. Blood for Vector Genome Determination

A blood sample will be collected at the time points specified in the Schedule of Events (Table 6) for the determination of vector genome (ie, DTX401) by [redacted]

8.3. Genotyping

8.3.1. Glucose-6-Phosphatase Genotyping

At Screening, subjects will be asked to provide a single whole-blood sample for *G6PC* genotyping. It is recommended that the Screening sample be collected at the time written informed consent is provided. The objective of this testing is to confirm the presence of a *G6PC* mutation and to provide an understanding of a potential relationship between genetic factors and the subject's response to DTX401. If genotyping results were previously documented from a qualified laboratory, these results can be used to satisfy the subject eligibility criteria.

8.4. Demographic and Other Assessments

8.4.1. Demographic, Medical, and GSDIa History Assessments

As allowed by local laws and regulations, the following demographic data may be captured on the appropriate page of the eCRF: year of birth, age, sex, ethnicity, and race.

Relevant medical and GSDIa history will be assessed as related to the eligibility criteria listed in Section 4.1 and Section 4.2. Medical condition or event, start date, end date, and status will be recorded on the appropriate page of the eCRF. The number of hospitalizations for hypoglycemic events (total and in the year prior to enrollment) will be collected and recorded on the appropriate page of the eCRF.

8.4.2. Assessment of Daily Prescribed Diet and Daily Diet Intake

The subject's daily prescribed diet and daily diet intake will be reviewed at the time points specified in the Schedule of Events (Table 6) and, if possible, on a weekly basis through the Week 52 visit or early withdrawal. Total calories, total carbohydrates and non-utilizable sugars, total protein, and total fat will be recorded on the appropriate page of the eCRF.

8.4.3. Assessment of Daily Prescribed Cornstarch (or Equivalent) and Daily Cornstarch (or Equivalent) Intake

The subject's daily prescribed cornstarch (or equivalent) and daily cornstarch (or equivalent) intake will be reviewed at the time points specified in the Schedule of Events (Table 6) and, if possible, on a weekly basis through the Week 52 visit or early withdrawal. Total daily cornstarch and frequency of intake will be recorded on the appropriate page of the eCRF.

9. SAFETY MONITORING AND REPORTING

9.1. Adverse Events and Serious Adverse Events

Adverse events will be assessed from the time the subject signs the ICF and for up to 30 days after the End of Study/Early Withdrawal visit. SAEs that occur more than 30 days after the End of Study/Early Withdrawal visit need not be reported unless the Investigator considers them related to study product.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being.

In addition to subject observations, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes) or from review of other documents that are relevant to subject safety will be documented on the AE page in the eCRF.

9.1.1. Definitions

9.1.1.1. Dose-Limiting Toxicity

A DLT is defined as any AE/SAE ≥ Grade 3 that is considered by the Investigator and/or Sponsor to be related to DTX401, based on NCI CTCAE Version 5.0 (NCI, 2018) or later version.

9.1.1.2. Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product (ie, DTX401) or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study, regardless of its causal relationship to study product. Subjects will be instructed to contact the Investigator at any time after the subject signs the ICF if any signs or symptoms develop.

Abnormal clinically significant laboratory values (clinical chemistry [including liver function tests], hematology, coagulation panel, and urinalysis) as assessed by the Investigator will be considered AEs.

A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study product or any event already present that worsens in either intensity or frequency after exposure to the study product.

9.1.1.3. Serious Adverse Events

An SAE is defined as any event that:

- Results in death
- Is immediately life threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or 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, or the development of drug dependency or drug abuse.

Nonemergent hospitalization for cornstarch management or glucose monitoring during steroid administration for vector-induced hepatitis (Section 8.2.6.2) will not be considered an SAE.

9.1.2. Safety Reporting

9.1.2.1. Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, Investigator-specified assessment of severity and relationship to study product, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

9.1.2.2. Serious Adverse Events

Any AE that meets SAE criteria (Section 9.1.1.3) or any of the safety stopping criteria (Section 3.2.4) must be reported by the study site to Ultragenyx immediately (ie, within 24 hours) after the time study site personnel first learn about the event (Table 3).

The study site should record all SAE information on the SAE page in the eCRF and submit the report via the electronic data capture (EDC) system. An event meeting any of the safety stopping criteria should only be reported as an SAE in the EDC if it meets the SAE criteria (Section 9.1.1.3).

If, for any reason, it is not possible to report the SAE in the EDC system (eg, the EDC system is unavailable), the study site should record the SAE on the paper SAE Reporting Form and fax or

email it to Ultragenyx (Table 3). Any SAE reported via fax or email must be entered into the EDC system as soon as it is possible.

Table 3: Ultragenyx Contact Information for SAE Reporting

Ultragenyx	**Email:** [redacted]
	Fax: [redacted]

9.1.2.2.1. Expedited Reporting

The Sponsor is responsible for reporting serious, unexpected, suspected adverse drug reactions (SUSARs) involving the study product to all regulatory authorities and participating investigators in accordance with International Council for Harmonisation (ICH) guidelines and/or local regulatory requirements, as applicable. It is the responsibility of the Investigator or designee to promptly notify the local institutional review board (IRB)/ independent ethics committee (IEC)/institutional biosafety committee (IBC) of all SUSARs involving risk to human subjects.

Due to the limited clinical experience with DTX401, reference safety information for assessing whether an AE is a SUSAR is currently not available. Therefore, any SAE considered related to DTX401 will be considered a SUSAR and reported immediately, as detailed in Section 9.1.2. The SAE should be treated with appropriate supportive and medical care deemed necessary for the well-being of the subject.

9.1.3. Assessment of Severity/Toxicity

The severity/toxicity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The Investigator should rate the intensity of an AE as Grade 1, 2, 3, 4, or 5 based on their medical judgment. The most current version of the NCI CTCAE can be used to guide the rating of an AE.

The CTCAE provides descriptive terminology that can be used to standardize AE reporting. A severity/toxicity grade is provided for each AE term that is grouped by the highest level of MedDRA classification. Specific symptoms and medical conditions have a clinical description for each level of severity/toxicity.

Increases in liver aminotransferase levels following DTX401 administration that are considered related to vector-induced hepatitis are expected, transient, asymptomatic, and self-limiting based on available evidence. If considered clinically significant in the Investigator's medical judgment (Section 8.2.6.2), these events should be recorded as an AE (Section 9.1.2.1) or SAE (Section 9.1.2.2) with an event term of elevated liver function tests and graded according to the general guidelines outlined in Table 4.

In the event that an AE occurs during the study that is not captured by the CTCAE, the AE should be graded according to the general guidelines outlined in Table 4.

Table 4: General Guidelines for Grading Events Not Captured by the CTCAE

Grade	Criteria
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a]
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity/toxicity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

9.1.4. Assessment of Causality

The Investigator's assessment of an AE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study product in causing or contributing to the AE will be characterized according to the classification and criteria outlined in Table 5.

Table 5: Classification and Criteria for AE Relationship to Study Product

Classification	Criteria
Unrelated	This relationship suggests that there is no association between the study product and the reported event.
Possible	This relationship suggests that treatment with the study product is causing or contributing to the AE; ie, the event follows a reasonable temporal sequence from the time of the study product administration or follows a known response pattern to the study product, but could also be produced by other factors.
Probable	This relationship suggests that a reasonable temporal sequence of the event with the study product administration exists and, based upon the known pharmacological action of the study product, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study product seems likely. The event disappears or decreases on cessation or reduction of the dose of study product.

Classification	Criteria
Unrelated	This relationship suggests that there is no association between the study product and the reported event.
Definite	This relationship suggests that a definite causal relationship exists between the study product administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study product is re-administered.

Abbreviation: AE = adverse event.

9.1.5. Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

9.2. Procedures for Handling Special Situations

9.2.1. Pregnancy and Birth Control

A serum pregnancy test will be performed on all female study subjects of childbearing potential during screening. A urine pregnancy test will be performed on all female study subjects of childbearing potential at each visit as specified in the Schedule of Events (Table 6).

Females of childbearing potential are defined as females physiologically capable of becoming pregnant. Females are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to enrollment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

Males and females of childbearing potential must be willing to use effective contraception at the time of administration of DTX401 and for 52 weeks following administration of DTX401 to prevent the potential transmission of the AAV vector. For male subjects, appropriate contraceptive methods include the use of a condom with spermicide. For female subjects, appropriate contraceptive methods include the use of a condom with spermicide plus at least 1 of the following:

- Hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device;
- Use of a diaphragm or cervical/vault cap; or
- Previous sterilization (surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) at least 6 weeks prior to DTX401 administration. In case of an oophorectomy alone, the reproductive status of the subject must have been confirmed by follow-up hormone level assessment.

Abstinence is an acceptable form of birth control; however, appropriate contraception must be used if the subject becomes sexually active. Abstinence is defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception. A condom with spermicide is required to be used by all sexually active vasectomized males in the study in order to prevent potential transmission of the vector via seminal fluid.

Pregnancy is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy in a female study subject that occurs during study participation must be reported using the paper Pregnancy Report Form. The study site should record the pregnancy on the paper Pregnancy Report Form and fax it to PrimeVigilance (Table 3). To ensure subject safety, each pregnancy in a female study subject must be reported to PrimeVigilance (contact information in Section 9.1.2.2) within 2 weeks of learning of its occurrence.

The pregnancy in a female study subject must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject discontinued from the study. Pregnancy complications and elective terminations for medical reasons should be reported as an AE or SAE. Spontaneous miscarriages or congenital abnormalities must be reported as an SAE. All neonatal deaths that occur within 28 days of birth should be reported as an SAE.

Any SAE occurring in association with a pregnancy in a female study subject brought to the Investigator's attention after the subject has completed the study, and considered by the Investigator as possibly related to the study product, must be promptly reported to Ultragenyx.

9.2.2. Treatment Noncompliance

9.2.2.1. Overdose Management

An overdose is any dose of the study product given to or taken by a subject that intentionally or unintentionally exceeds the dose, based on body weight (kg), described in Section 3.1. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported in the appropriate AE or SAE page of the eCRF. The actual dose infused will be recorded on the appropriate page of the eCRF.

There is no treatment for overdose. All subjects will be closely monitored at the time of infusion for any adverse effects, and supportive care will be administered at the discretion of the Investigator, as needed, should an overdose be suspected.

9.2.2.2. Medication Errors

A medication error is defined as a mistake made in prescribing, dispensing, administration, or use of the study product. The treatment will be open-label and is to be administered by trained medical personnel at the study site.

9.3. Data Monitoring Committee

An independent DMC will be responsible for monitoring safety data from the study. For Cohorts 1 and 2, the DMC met after all evaluable subjects in the dosing cohort completed Week 12 of the study to review the safety data and provide their recommendation for progressing to the next dosing cohort or enrollment of subjects into additional cohorts.

The DMC will meet at the end of the study and may, at any time, recommend modifying or pausing enrollment due to safety concerns based on their periodic data reviews. Additionally, if an Investigator reports an AE/SAE that meets any of the safety stopping criteria (Section 3.2.4), enrollment will be paused and the DMC will meet to review available data. If a decision is made to resume enrollment, this decision will be communicated to and, if required, approved by regulatory authorities according to country requirements.

The DMC comprises 2 independent medical professionals and an independent biostatistician who are qualified to review the data and provide recommendations for progressing to the next dosing level or enrollment of subjects into additional cohorts. The DMC charter details the members' roles and responsibilities as part of the DMC, the process for each data review (scheduled or ad hoc), and the full scope of each review.

10. STATISTICAL AND ANALYTICAL PLAN

A statistical analysis plan (SAP) will be written and will provide a detailed description of the statistical methods and expand on the details provided in this protocol. Additional analyses may be added.

10.1. Endpoints

The primary, secondary, and exploratory endpoints are detailed in Section 2.

The following general analysis summaries and listings will be conducted for subjects who receive at least 1 dose of study drug. The MTD dose escalation evaluation will be performed for MTD evaluable subjects. Statistical analysis sets for all the tables, listings, and figures will be defined in the SAP.

10.2. Statistical Analysis Methodology

The CRM model will be used to evaluate each dose for dose escalation using software FACTS (Berry Consultants, Austin, Texas, United States) Version 6.0 or later. The OBD will be based on the MTD and an assessment of clinical benefit. SAS® software (SAS Institute, Inc, Cary, North Carolina, United States) Version 9.2 or later will be used for general data presentation and statistical analyses. Continuous variables will be summarized using the mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions will be described in the SAP.

10.2.1. The Continual Reassessment Method

Neuenschwander's CRM (or nCRM) (Neuenschwander et al., 2008) will be used to make recommendations for the dose to be administered in each cohort using all evaluable subjects (ie, subjects who remain in the study for at least 12 weeks after dosing or for whom a DLT is observed within 12 weeks of dosing). The DLT assessment for each subject is based on the definition in Section 9.1.1.1. The DLT evaluation window for each subject starts on the date of administration of DTX401 and continues for up to 12 weeks (84 days) thereafter, or until all Week 12 safety assessments have been completed, whichever occurs later.

The target toxicity rate is 0.25. The cohort size is 3 subjects. The dose levels that may be studied are specified in Section 3.1. The first cohort will be treated at 2×10^{12} GC/kg. Subsequent doses will be treated at the lower of the current estimate of the MTD and the highest dose allowed by the escalation rule.

A logistic model will be used to model the dose-toxicity curve; further details on that are provided in Section 15.2, Appendix 2.

The CRM model will recommend that the study is stopped for having the MTD determined the first time any of the following criteria are satisfied after a CRM model update:

- Six evaluable subjects have been treated at 1×10^{13} GC/kg and the current estimate of the MTD is $> 1 \times 10^{13}$ GC/kg
- Six evaluable subjects have been treated at the current estimate of the MTD
- The current estimate of the MTD is $< 2 \times 10^{12}$ GC/kg (insufficient safety)

The study will stop when the maximum sample size of 12 subjects have been enrolled or at the Sponsor's discretion. If 12 subjects have been enrolled and the definition of having an MTD determined has not been reached, then the highest dose considered at or below the MTD will be considered the MTD.

Enrollment will be limited so that each dosing cohort initially includes no more than 3 subjects. A cohort may be expanded to include additional subjects to confirm the findings for the cohort.

10.2.2. Sample Size Justification

Simulations (result on file at PPD) show that if all 3 doses are safe and no DLTs occur, the CRM will recommend dose escalation to 1×10^{13} GC/kg (genome copies measured by [redacted]) and the recruitment of 12 subjects. Based on safety and efficacy observations in Cohorts 1, 2, and 3 (3 subjects each) and a positive recommendation from the DMC, it was decided to enroll a fourth cohort of 3 subjects. The planned sample size of the study will therefore be 12 subjects including 4 cohorts.

The protocol allows multiple cohorts to be enrolled to assess varied oral steroid regimens to manage the mild, asymptomatic elevations in liver aminotransferase levels that have been observed following DTX401 administration (Derks et al., 2019; Weinstein et al., 2019). The CRM model will evaluate subjects based on the dose administered regardless of the steroid approach used (ie, reactive vs prophylactic).

10.2.3. Efficacy Analyses

10.2.3.1. Symptom-Free Euglycemia

The time (in minutes) to the first hypoglycemic event (defined as glucose < 54 mg/dL [< 3.0 mmol/L]) during a controlled fasting challenge will be determined for all subjects at Day 0 and Weeks 12, 24, and 52. Full details of the analysis will be provided in the SAP.

10.2.3.2. Continuous Glucose Monitoring

Continuous glucose monitoring device data will be summarized in tables, figures and provided in the listings. All analyses details will be specified in the SAP.

10.2.3.3. Use of Cornstarch (or Equivalent)

Use (both quantity and frequency) of cornstarch over time will be summarized in tables, figures and provided in the listings. All analyses details will be specified in the SAP.

10.2.3.4. Morning Glucose Levels

Morning glucose levels will be summarized in a table and provided in the listings.

10.2.3.5. [redacted]

[redacted]

10.2.3.6. [redacted]

[redacted]

10.2.4. Safety Analyses

All subjects who receive DTX401 will be included in the safety analysis.

10.2.4.1. Adverse Events

With the exception of the CRM modelling described above, all statistical analyses of safety outcomes will be descriptive. The incidence of AEs and TEAEs will be summarized by system organ class and preferred term. Additionally, TEAEs may be summarized for each dose by severity and relationship to study product, if applicable. SAEs will be presented for each dose by relationship to study product. Summary tables will present the total number of TEAEs as well as the number of subjects with TEAE incidence by system organ class and preferred term. For summaries of TEAEs, subjects experiencing an event more than once with varying severity will be counted only once, using only the maximum severity observed within each system organ class and preferred term. For incidence of relationship to study product, subjects will be counted only once, in the category of the strongest relationship to study product within each system organ class and preferred term.

10.2.4.2. Physical Examination Findings

Complete and targeted physical examination findings will be summarized by visit and dose.

10.2.4.3. Vital Sign Measurements

Vital sign measurements (heart rate, blood pressure [systolic and diastolic], and respiratory rate) will be summarized over time in terms of absolute values and changes from Baseline by visit and dosing cohort. Height and weight will be summarized.

10.2.4.4. Electrocardiogram Results

Electrocardiogram data will be summarized by visit and dosing cohort. Each ECG will be classified as “abnormal” or “normal,” and the relevance of the abnormality will be summarized as “clinically significant” or “not clinically significant.”

10.2.4.5. Hypoglycemic Events

The number of symptomatic hypoglycemic events will be summarized by dose level of DTX401. Hypoglycemic events reported by the subject will be summarized separately for each dose of DTX401.

10.2.4.6. Clinical Laboratory Assessment Results

For all clinical laboratory parameters (Section 8.2.6.1) with continuous results, absolute values and changes from Baseline will be summarized by visit and dosing cohort. For laboratory parameters with categorical results, shifts from Baseline will be summarized by visit and dosing cohort. Laboratory values from the central laboratory and local laboratories will be analyzed.

10.2.4.7. Other Laboratory Results

Neutralizing antibodies to AAV8, cell-mediated immune response to AAV8 and G6Pase, AAV8 binding antibody IgG assay, anti-G6Pase antibody assay, vector shedding, and vector genome determination will be summarized by time point and dosing cohort. Associations between these parameters and dose will be undertaken using tabular summaries and appropriate statistical methods, as will be outlined in the SAP.

10.2.5. Other Analyses

Demographics and other background information will be summarized by dose group. Background information includes prior medications, medical conditions, GSDIa medical history (including number of hospitalizations for hypoglycemic events [total and in the year prior to enrollment]). Current medical conditions and concomitant medications will be summarized. A summary of subject disposition and treatment exposure will be prepared.

Other data described in Section 8.4 will be summarized accordingly, including assessments of prescribed diet (including daily carbohydrate intake).

10.2.6. Interim Analysis

An interim analysis will be conducted when a minimum of 12-week data are available for all subjects from at least 2 dosing cohorts. Additional interim analyses may be conducted at the Sponsor’s discretion. Results and their dissemination will be at the Sponsor’s discretion. A detailed plan for the analysis of the safety and efficacy data will be presented in the SAP.

10.3. Data Quality Assurance

Study sites will maintain source documentation and enter subject data in the eCRF as accurately as possible and will rapidly respond to any reported discrepancies. The eCRFs are accessed through Oracle Health Sciences InForm. This EDC system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11. Each person involved with the study will have an individual username and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. A quality review of the data will be performed by the study site with additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by study site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling study site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the Investigator. This system provides study site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and Investigator comment information.

After all queries have been resolved, the SAP is approved and signed, and any summary/analysis populations are approved, the database will be locked. All summary and analysis of the data will be performed using SAS software Version 9.2 or later.

10.3.1. Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, and other materials.

The Sponsor (or Sponsor designee) will supply the eCRF. Study personnel must have documented training of the use of the EDC system before the system can be authorized.

All eCRF information is to be completed. If an item is not available or is not applicable, this fact should be indicated.

Study site personnel will enter subject data into the EDC system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data). All entries and changes to the data in the eCRF will be recorded electronically with an audit trail specifying the date and time of entry or change and the name of the authorized person making the entry or change. The Investigator will answer all queries issued, if applicable. Data queries and query correspondence will be included in the audit trail.

Clinical data management will be performed in accordance with applicable Sponsor (or Sponsor designee) standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and concomitant medication terms will be coded using MedDRA and WHO Drug dictionary terminology, respectively.

After database lock, each study site will receive an electronic copy of their study site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, an electronic copy of all of the study site's data from the study will be created and sent to the Sponsor for storage. The Sponsor (or Sponsor designee) will maintain a duplicate electronic copy for their records. In all cases, subject initials will not be collected or transmitted to the Sponsor.

11. ETHICS

11.1. Institutional Review Board, Independent Ethics Committee, and Institutional Biosafety Committee

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC/IBC before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by an IRB/IEC/IBC. Documentation of all IRB/IEC/IBC approvals and of the IRB/IEC/IBC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) will be maintained by the study site and will be available for review by the Sponsor or its designee.

All IRB/IEC/IBC approvals should be signed by the IRB/IEC/IBC chair or designee and must identify the IRB/IEC/IBC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC/IBC. The Investigator must promptly supply the Sponsor or its designee, the IRB/IEC/IBC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

11.2. Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable local laws and regulations.

11.3. Subject Information and Consent

A written ICF in compliance with regulatory authority regulations and 21 CFR §50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An ICF template may be provided by the Sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the ICF should be reviewed by the Sponsor, its designee, or both before IRB/IEC/IBC submission. Once reviewed, the ICF will be submitted by the Investigator to his or her IRB/IEC/IBC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or their legal guardian will be given a full explanation of the study and be given the opportunity to read the approved ICF. Once the Investigator is assured that the subject or their legal guardian understands the implications of participating in the study, the subject or their legal guardian will be asked to give consent to participate in the study by signing the ICF.

The Investigator shall retain the signed original ICF(s) and must provide a copy of the signed original form to the subject or their legal guardian.

12. INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Any change will be reported to the IRB/IEC/IBC but will not require a protocol amendment.

12.1. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA, other applicable regulatory agencies, or the IRB/IEC/IBC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

12.2. Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR §54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor PPD is financially responsible for further treatment of the subject's disease.

12.3. Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC/IBC approvals
- Original Investigator-signed Investigator agreement page of the protocol
- Form FDA 1572 (or equivalent), fully executed, and all updates on a new fully executed Form FDA 1572 (or equivalent)
- Curriculum vitae for the Investigator and each Subinvestigator
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR §54. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC/IBC-approved ICF, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or their legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the study site, in accordance with 42 CFR §493

12.4. Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of subjects begins.

12.5. Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

12.6. Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC/IBC, as appropriate.

12.7. Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB/IEC/IBC with a summary of the study's outcome and the Sponsor and regulatory authorities with any reports required.

12.8. Record Retention

For study monitoring, audit, or inspection, the IRB/IEC and Sponsor or its designees have the right to access all CRFs, source documents, and other study documentation. The Investigator or study site will retain such documents from the start of the study to at least 25 years after the close of the study, guarantee access to these documents, and cooperate with and support such audits and inspections.

12.9. Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

13. STUDY MANAGEMENT

The administrative structure will include a DMC (Section 9.3).

13.1. Monitoring

13.1.1. Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to closely follow the progression of the study, ensuring that it is being conducted in compliance with the protocol, ICH E6(R2), all applicable local laws and regulations, and with current and applicable standard operating procedures. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and written contact.
The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and study site personnel.

13.1.2. Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC/IBC review, and regulatory inspections by providing direct access to all study records. In the event of either an audit or inspection, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The Investigator should promptly notify the clinical research associate of any audits or inspections scheduled by any regulatory authorities and promptly forward copies of any reports received to the clinical research associate. The clinical research associate will then inform and forward any reports to the Sponsor.

13.2. Management of Protocol Amendments and Deviations

13.2.1. Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC/IBC for approval before subjects can be enrolled into an amended protocol.

13.2.2. Protocol Deviations

A deviation from the protocol is a departure from the written procedures or processes.
A significant deviation occurs when there is nonadherence to the protocol by the subject or Investigator that results in a significant, additional risk to the subject or important change to the study design. Significant deviations can include nonadherence to inclusion or exclusion criteria, nonadherence to safety and efficacy-related assessments, or nonadherence to FDA regulations or ICH GCP guidelines, that could lead to the subject being withdrawn from the study (Section 7.1).

Protocol waivers or exemptions are not permitted. Adherence to the study design requirements, including those specified in the Schedule of Events (Table 6), is essential for study conduct.

The Investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC/IBC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC/IBC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal Investigators will be notified in writing by the monitor of deviations. The IRB/IEC/IBC should be notified of all protocol deviations in a timely manner, as required.

13.3. Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

13.4. Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study report (CSR) is prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. The Sponsor will also ensure that the CSR in marketing applications meets the standards of the ICH harmonised tripartite guideline E3: Structure and Content of CSRs.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, the Sponsor will provide the Investigator with a summary of the cumulative study results. The Investigator is encouraged to share the cumulative summary results and will provide each subject with their individual data. The study results will be posted on publicly available clinical study registers, where required.

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 1/2, Open-Label Safety and Dose-Finding Study 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)"

I have read and agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 6.0, dated 28 October 2019, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations and inform all who assist me in the conduct of this study of their responsibilities and obligations.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

14. REFERENCE LIST

Bali DS, Chen YT, Austin S, et al. (2016) Glycogen Storage Disease Type I. In: Adam MP, Ardinger HH, Pagon RA, et al. (eds) *GeneReviews((R)).* Seattle (WA).

Beaty RM, Jackson M, Peterson D, et al. (2002) Delivery of glucose-6-phosphatase in a canine model for glycogen storage disease, type Ia, with adeno-associated virus (AAV) vectors. *Gene Ther* 9: 1015-1022.

Bhattacharya K, Orton RC, Qi X, et al. (2007) A novel starch for the treatment of glycogen storage diseases. *J Inherit Metab Dis* 30: 350-357.

Boers SJ, Visser G, Smit PG, et al. (2014) Liver transplantation in glycogen storage disease type I. *Orphanet J Rare Dis* 9: 47.

Boutin S, Monteilhet V, Veron P, et al. (2010) Prevalence of serum IgG and neutralizing factors against adeno-associated virus (AAV) types 1, 2, 5, 6, 8, and 9 in the healthy population: implications for gene therapy using AAV vectors. *Hum Gene Ther* 21: 704-712.

Calcedo R and Wilson JM. (2013) Humoral Immune Response to AAV. *Front Immunol* 4: 341.

Chen YT, Coleman RA, Scheinman JI, et al. (1988) Renal disease in type I glycogen storage disease. *N Engl J Med* 318: 7-11.

CHMP. (2009) Guideline on follow-up of patients administered with gene therapy medicinal products. EMEA Doc Ref. EMEA/CHMP/GTWP/60436/2007. London: European Medicines Agency.

Chou JY. (2001) The molecular basis of type 1 glycogen storage diseases. *Curr Mol Med* 1: 25-44.

Chou JY and Mansfield BC. (1999) Molecular Genetics of Type 1 Glycogen Storage Diseases. *Trends Endocrinol Metab* 10: 104-113.

Chou JY and Mansfield BC. (2007) Gene therapy for type I glycogen storage diseases. *Curr Gene Ther* 7: 79-88.

Chou JY and Mansfield BC. (2011) Recombinant AAV-directed gene therapy for type I glycogen storage diseases. *Expert Opin Biol Ther* 11: 1011-1024.

Davidoff AM, Gray JT, Ng CY, et al. (2005) Comparison of the ability of adeno-associated viral vectors pseudotyped with serotype 2, 5, and 8 capsid proteins to mediate efficient transduction of the liver in murine and nonhuman primate models. *Mol Ther* 11: 875-888.

Davis MK and Weinstein DA. (2008) Liver transplantation in children with glycogen storage disease: controversies and evaluation of the risk/benefit of this procedure. *Pediatr Transplant* 12: 137-145.

Derks TG, Ahmad A, Rodriguez-Buritica D, et al. (2019) Positive cohort 1 results from the phase 1/2, AAV8-mediated liver-directed gene therapy trial in glycogen storage disease type Ia (GSDIa). *J Inherit Metab Dis* 42: 7.

ECDC. (2017) *ECDC Vaccine Scheduler*. Available at: https://www.ecdc.europa.eu/en/publications-data/ecdc-vaccine-scheduler.

Ezeanolue E, Harriman K, Hunter P, et al. (2020) *General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP).* Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.

FDA. (2006) Guidance for Industry: Gene therapy clinical trials - observing subjects for delayed adverse events. U.S. Department of Health and Human Services Food and Drug Administration.

FDA. (2015) Guidance for industry: Considerations for the design of early-phase clinical trials of cellular and gene therapy products.

Foster JD and Nordlie RC. (2002) The biochemistry and molecular biology of the glucose-6-phosphatase system. *Exp Biol Med (Maywood)* 227: 601-608.

Franco LM, Krishnamurthy V, Bali D, et al. (2005) Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. *J Inherit Metab Dis* 28: 153-162.

Gao G, Vandenberghe LH and Wilson JM. (2005) New recombinant serotypes of AAV vectors. *Curr Gene Ther* 5: 285-297.

Gao G, Wang Q, Calcedo R, et al. (2009) Adeno-associated virus-mediated gene transfer to nonhuman primate liver can elicit destructive transgene-specific T cell responses. *Hum Gene Ther* 20: 930-942.

Gao GP, Alvira MR, Wang L, et al. (2002) Novel adeno-associated viruses from rhesus monkeys as vectors for human gene therapy. *Proc Natl Acad Sci U S A* 99: 11854-11859.

Ghosh A, Allamarvdasht M, Pan CJ, et al. (2006) Long-term correction of murine glycogen storage disease type Ia by recombinant adeno-associated virus-1-mediated gene transfer. *Gene Ther* 13: 321-329.

Herzog RW, Mount JD, Arruda VR, et al. (2001) Muscle-directed gene transfer and transient immune suppression result in sustained partial correction of canine hemophilia B caused by a null mutation. *Mol Ther* 4: 192-200.

Jiang H, Couto LB, Patarroyo-White S, et al. (2006) Effects of transient immunosuppression on adenoassociated, virus-mediated, liver-directed gene transfer in rhesus macaques and implications for human gene therapy. *Blood* 108: 3321-3328.

Kishnani PS, Austin SL, Arn P, et al. (2010) Glycogen storage disease type III diagnosis and management guidelines. *Genet Med* 12: 446-463.

Koeberl DD, Pinto C, Brown T, et al. (2009) Gene therapy for inhereted metabolic disorders in companion animals. *ILAR J* 50: 122-127.

Koeberl DD, Pinto C, Sun B, et al. (2008) AAV vector-mediated reversal of hypoglycemia in canine and murine glycogen storage disease type Ia. *Mol Ther* 16: 665-672.

Koeberl DD, Sun B, Bird A, et al. (2007) Efficacy of helper-dependent adenovirus vector-mediated gene therapy in murine glycogen storage disease type Ia. *Mol Ther* 15: 1253-1258.

Koeberl DD, Sun BD, Damodaran TV, et al. (2006) Early, sustained efficacy of adeno-associated virus vector-mediated gene therapy in glycogen storage disease type Ia. *Gene Ther* 13: 1281-1289.

Lee YM, Jun HS, Pan CJ, et al. (2012) Prevention of hepatocellular adenoma and correction of metabolic abnormalities in murine glycogen storage disease type Ia by gene therapy. *Hepatology* 56: 1719-1729.

Lei KJ, Chen YT, Chen H, et al. (1995a) Genetic basis of glycogen storage disease type 1a: prevalent mutations at the glucose-6-phosphatase locus. *Am J Hum Genet* 57: 766-771.

Lei KJ, Pan CJ, Liu JL, et al. (1995b) Structure-function analysis of human glucose-6-phosphatase, the enzyme deficient in glycogen storage disease type 1a. *J Biol Chem* 270: 11882-11886.

Lei KJ, Shelly LL, Lin B, et al. (1995c) Mutations in the glucose-6-phosphatase gene are associated with glycogen storage disease types 1a and 1aSP but not 1b and 1c. *J Clin Invest* 95: 234-240.

Lei KJ, Shelly LL, Pan CJ, et al. (1993) Mutations in the glucose-6-phosphatase gene that cause glycogen storage disease type 1a. *Science* 262: 580-583.

Li C, Hirsch M, Asokan A, et al. (2007a) Adeno-associated virus type 2 (AAV2) capsid-specific cytotoxic T lymphocytes eliminate only vector-transduced cells coexpressing the AAV2 capsid in vivo. *J Virol* 81: 7540-7547.

Li H, Murphy SL, Giles-Davis W, et al. (2007b) Pre-existing AAV capsid-specific CD8+ T cells are unable to eliminate AAV-transduced hepatocytes. *Mol Ther* 15: 792-800.

Manno CS, Chew AJ, Hutchison S, et al. (2003) AAV-mediated factor IX gene transfer to skeletal muscle in patients with severe hemophilia B. *Blood* 101: 2963-2972.

Manno CS, Pierce GF, Arruda VR, et al. (2006) Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. *Nat Med* 12: 342-347.

Matern D, Starzl TE, Arnaout W, et al. (1999) Liver transplantation for glycogen storage disease types I, III, and IV. *Eur J Pediatr* 158 Suppl 2: S43-48.

Mingozzi F and High KA. (2011) Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges. *Nat Rev Genet* 12: 341-355.

Mingozzi F, Maus MV, Hui DJ, et al. (2007) CD8(+) T-cell responses to adeno-associated virus capsid in humans. *Nat Med* 13: 419-422.

Mount JD, Herzog RW, Tillson DM, et al. (2002) Sustained phenotypic correction of hemophilia B dogs with a factor IX null mutation by liver-directed gene therapy. *Blood* 99: 2670-2676.

Mutel E, Abdul-Wahed A, Ramamonjisoa N, et al. (2011) Targeted deletion of liver glucose-6 phosphatase mimics glycogen storage disease type 1a including development of multiple adenomas. *J Hepatol* 54: 529-537.

Nakai H, Yant SR, Storm TA, et al. (2001) Extrachromosomal recombinant adeno-associated virus vector genomes are primarily responsible for stable liver transduction in vivo. *J Virol* 75: 6969-6976.

Nathwani AC, Gray JT, McIntosh J, et al. (2007) Safe and efficient transduction of the liver after peripheral vein infusion of self-complementary AAV vector results in stable therapeutic expression of human FIX in nonhuman primates. *Blood* 109: 1414-1421.

Nathwani AC, Gray JT, Ng CY, et al. (2006) Self-complementary adeno-associated virus vectors containing a novel liver-specific human factor IX expression cassette enable highly efficient transduction of murine and nonhuman primate liver. *Blood* 107: 2653-2661.

Nathwani AC, Reiss UM, Tuddenham EG, et al. (2014) Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med* 371: 1994-2004.

Nathwani AC, Rosales C, McIntosh J, et al. (2011a) Long-term safety and efficacy following systemic administration of a self-complementary AAV vector encoding human FIX pseudotyped with serotype 5 and 8 capsid proteins. *Mol Ther* 19: 876-885.

Nathwani AC, Tuddenham EG, Rangarajan S, et al. (2011b) Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med* 365: 2357-2365.

NCI. (2018) National Cancer Institute Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS). Common Terminology Criteria for Adverse Events V4.3 (CTCAE). Available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50.

Neuenschwander B, Branson M and Gsponer T. (2008) Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med* 27: 2420-2439.

Nichols TC, Raymer RA, Franck HW, et al. (2010) Prevention of spontaneous bleeding in dogs with haemophilia A and haemophilia B. *Haemophilia* 16 Suppl 3: 19-23.

Pan CJ, Lei KJ, Chen H, et al. (1998) Ontogeny of the murine glucose-6-phosphatase system. *Arch Biochem Biophys* 358: 17-24.

Public Health England. (2017) *Immunisation against infectious disease : The Green Book. Chapter 6, Contraindications and special considerations.* Available at: https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6.

Public Health England. (2020) Immunisation against infectious disease : The Green Book, Chapter 7, Immunisation of individuals with underlying medical conditions:.

Reddy SK, Kishnani PS, Sullivan JA, et al. (2007) Resection of hepatocellular adenoma in patients with glycogen storage disease type Ia. *J Hepatol* 47: 658-663.

Rubin LG, Levin MJ, Ljungman P, et al. (2014) 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 58: e44-100.

Siders WM, Shields J, Kaplan J, et al. (2009) Cytotoxic T lymphocyte responses to transgene product, not adeno-associated viral capsid protein, limit transgene expression in mice. *Hum Gene Ther* 20: 11-20.

Snyder RO, Miao C, Meuse L, et al. (1999) Correction of hemophilia B in canine and murine models using recombinant adeno-associated viral vectors. *Nat Med* 5: 64-70.

Sun MS, Pan CJ, Shieh JJ, et al. (2002) Sustained hepatic and renal glucose-6-phosphatase expression corrects glycogen storage disease type Ia in mice. *Hum Mol Genet* 11: 2155-2164.

uniQure. (2014) uniQure: Hemophilia -- the challenge for gene therapy. Talk preesented at Investor Day; December 1, 2014; New York City, NY. Data on file. Accessed November 1, 2016.

uniQure. (2015) Corzo D. Gene Therapy for Liver Disease and Metabolic Disorder. Talk presented at uniQure R&D Day; October 15, 2015; New York City, NY. Data on file. Accessed November 1, 2016.

uniQure. (2016) Corzo D. Interim Topline Results from Hemophilia B Phase I/II Study AMT-060-01 in Hemophilia B. Webcast. January 7, 2016: Data on file. Accessed November 1, 2016.

van Schaftingen E and Gerin I. (2002) The glucose-6-phosphatase system. *Biochem J* 362: 513-532.

Vandenberghe LH, Wang L, Somanathan S, et al. (2006) Heparin binding directs activation of T cells against adeno-associated virus serotype 2 capsid. *Nat Med* 12: 967-971.

Wang D, Pascual JM and De Vivo D. (2012) Glucose Transporter Type 1 Deficiency Syndrome. In: Pagon RA, Adam MP, Bird TD, et al. (eds) *GeneReviews.* Seattle (WA).

Wang L, Calcedo R, Nichols TC, et al. (2005) Sustained correction of disease in naive and AAV2-pretreated hemophilia B dogs: AAV2/8-mediated, liver-directed gene therapy. *Blood* 105: 3079-3086.

Wang L, Figueredo J, Calcedo R, et al. (2007) Cross-presentation of adeno-associated virus serotype 2 capsids activates cytotoxic T cells but does not render hepatocytes effective cytolytic targets. *Hum Gene Ther* 18: 185-194.

Weinstein DA, Ahmad A, C. L, et al. (2019) Positive cohort 1 results from the phase 1/2 trial with AAV8-mediated liver-directed gene therapy in adults with glycogen storage disease type Ia. *Molecular Therapy* 27: 12.

Weinstein DA, Correia CE, Conlon T, et al. (2010) Adeno-associated virus-mediated correction of a canine model of glycogen storage disease type Ia. *Hum Gene Ther* 21: 903-910.

Wolfsdorf JI and Crigler JF, Jr. (1997) Cornstarch regimens for nocturnal treatment of young adults with type I glycogen storage disease. *Am J Clin Nutr* 65: 1507-1511.

Wolfsdorf JI, Holm IA and Weinstein DA. (1999) Glycogen storage diseases. Phenotypic, genetic, and biochemical characteristics, and therapy. *Endocrinol Metab Clin North Am* 28: 801-823.

Wolfsdorf JI, Laffel LM and Crigler JF, Jr. (1997) Metabolic control and renal dysfunction in type I glycogen storage disease. *J Inherit Metab Dis* 20: 559-568.

Yan Z, Zak R, Luxton GW, et al. (2002) Ubiquitination of both adeno-associated virus type 2 and 5 capsid proteins affects the transduction efficiency of recombinant vectors. *J Virol* 76: 2043-2053.

Yiu WH, Lee YM, Peng WT, et al. (2010) Complete normalization of hepatic G6PC deficiency in murine glycogen storage disease type Ia using gene therapy. *Mol Ther* 18: 1076-1084.

15. APPENDICES

15.1. Appendix 1: Schedule of Events

Table 6: Schedule of Events – Scheduled Study Visits

Period	SV[a]	BL	Dosing		Follow-up Period																					EOS/ EW
Visit Time (Day/Week)	D−56 to D−1	D0	D1		D4	D8	D12	D16	D20	D24	D28	D32	D36	D39	D42	D45	D48	D52	D56	D60	D64	D68	D72	D76	D80	D84	D168	D252	D365
			Predose	Dosing/ Postdose							W4				W6											W12	W24	W36	W52
Visit Window (Days)	–	–	–	–	±1						±2	±1			±2	±1										±2	±7	±7	±7
Visit Type	OP	IP			OP/HH						OP	OP/HH			OP	OP/HH										IP[dd]	IP	OP	IP
Informed consent	X																												
Eligibility criteria	X	X																											
Admission to study site or hospital		X																								X	X		X
Demographics	X																												
Relevant medical history	X																												
GSDIa medical history	X																												
Height	X																												
Weight	X	X													X											X	X	X	X
Relevant prior medications/ therapies/ procedures	X																												
Relevant concomitant medications/ therapies/ procedures		X	X	X							X				X											X	X	X	X
Health-related Quality of Life [redacted]																													
[redacted]		X																								X	X		X
GSDIa Morning Diary[b,c]		X																								X	X		X
GSDIa Evening Diary[b,c]		X																								X	X		X
[redacted]																											X		X
Subject interview																											X[d]		X[d]

Period	SV[a]	BL	Dosing		Follow-up Period																						EOS/ EW
Visit Time (Day/Week)	D−56 to D−1	D0	D1		D4	D8	D12	D16	D20	D24	D28	D32	D36	D39	D42	D45	D48	D52	D56	D60	D64	D68	D72	D76	D80	D84	D168	D252	D365
			Predose	Dosing/ Postdose							W4				W6											W12	W24	W36	W52
Visit Window (Days)	–	–	–	–	±1						±2	±1			±2	±1										±2	±7	±7	±7
Visit Type	OP	IP			OP/HH						OP	OP/HH			OP	OP/HH										IP[dd]	IP	OP	IP
Safety Assessments																													
AE/SAE monitoring	X	X	X	X							X				X											X	X	X	X
Assessment of symptomatic hypoglycemic events	X	X	X	X							X				X											X	X	X	X
Vital sign measurement (HR, BP, RR)	X	X	X	X[e]							X				X											X	X	X	X
Complete physical examination[f]	X																												X
Targeted physical examination[g]		X									X				X											X	X	X	
12-lead ECG	X	X	X																										X
Laboratory Assessments																													
G6PC genotyping	X[h]																												
HBV, HCV, HIV status	X																												
Serum pregnancy test (females of childbearing potential only)	X																												
Urine pregnancy test (females of childbearing potential only)		X																								X	X		X
Clinical chemistry (includes lipid panel and LFTs [LFT STAT sample])[i]	X[j]	X[k]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X[k]	X	X[k]
Hematology	X	X									X				X											X	X	X	X
Coagulation panel	X	X									X				X											X	X	X	X
Urinalysis	X	X									X				X											X	X	X	X
Cortisol, fatty acid, glucagon, insulin, C-peptide, growth hormone, IGFBP1, ACTH, alanine, and ketone blood levels[m]		X																								X[n]	X		X

Period	SV[a]	BL	Dosing		Follow-up Period																						EOS/ EW
Visit Time (Day/Week)	D−56 to D−1	D0	D1		D4	D8	D12	D16	D20	D24	D28	D32	D36	D39	D42	D45	D48	D52	D56	D60	D64	D68	D72	D76	D80	D84	D168	D252	D365
			Predose	Dosing/ Postdose							W4				W6											W12	W24	W36	W52
Visit Window (Days)	–	–	–	–	±1						±2	±1			±2	±1										±2	±7	±7	±7
Visit Type	OP	IP			OP/HH						OP	OP/HH			OP	OP/HH										IP[dd]	IP	OP	IP
[redacted]		X																								X	X		X
[redacted]	X[o]	X									X				X											X	X	X	X
[redacted]	X	X									X				X											X	X	X	X
[redacted]		X			X		X		X		X		X		X		X		X		X		X		X	X	X	X	X
[redacted]		X																								X			X
[redacted]			X	X[p]							X				X											X	X	X	X
[redacted]		X			X		X		X		X		X		X		X		X		X		X		X	X	X[q]	X[q]	X[q]
[redacted]																													
[redacted]	X																												
[redacted]		X																								X	X		X
Diet and Cornstarch Assessments																													
Assessment of prescribed diet and dietary intake[r]	X	X[s]									X				X[s]											X[s]	X[s]	X	X[s]
Assessment of cornstarch (or equivalent) intake[t]	X	X									X				X											X	X	X	X

Period	SV[a]	BL	Dosing		Follow-up Period																						EOS/ EW
Visit Time (Day/Week)	D−56 to D−1	D0	D1		D4	D8	D12	D16	D20	D24	D28	D32	D36	D39	D42	D45	D48	D52	D56	D60	D64	D68	D72	D76	D80	D84	D168	D252	D365
			Predose	Dosing/ Postdose							W4				W6											W12	W24	W36	W52
Visit Window (Days)	–	–	–	–	±1						±2	±1			±2	±1										±2	±7	±7	±7
Visit Type	OP	IP			OP/HH						OP	OP/HH			OP	OP/HH										IP[dd]	IP	OP	IP
Glucose Monitoring																													
Provide CGM device to subject[u]	X																												
Distribute and collect Morning Glucose Level monitoring worksheet[v]				X							X				X											X	X	X	X
Assessment of morning glucose levels[w]											X				X											X	X	X	X
Controlled Fasting Challenge Assessments																													
Dinner before controlled fasting challenge[x]		X																								X	X		X
Cornstarch dose prior to starting controlled fasting challenge[y]		X																								X	X		X
Controlled fasting challenge[z]		X																								X	X		X
Glucose, lactate, growth hormone, IGFBP1 cortisol, and ACTH blood levels (local laboratory; 30 min after the end of the fasting challenge)		X																								X	X		X
Glucose and lactate (venous) sample (local laboratory [STAT sample])[aa]		X																								X	X		X
Screening, Enrollment, and Infusion																													
IWRS[bb]	X	X																											
DTX401 infusion[cc]				X																									

Abbreviations: AAV8 = adeno-associated virus serotype 8; ACTH= adrenocorticotropic hormone, AE = adverse event; BL = Baseline; BP = blood pressure; CGM = continuous glucose monitoring; D = day; ECG = electrocardiogram; [redacted] EOS = end of study; EW = early withdrawal; G6Pase = glucose-6-phosphatase (protein); *G6PC* = glucose-6-phosphatase (gene); GSDIa = glycogen storage disease type Ia;

HBV = hepatitis B virus; HCV = hepatitis C virus; HH = home visit; HIV = human immunodeficiency virus; HR = heart rate; IGFBP1 = insulin-like growth factor-binding protein 1; IgG = immunoglobulin G; IP = inpatient study visit; IWRS = interactive web response system; LFTs = liver function tests; [redacted] nAb = neutralizing antibody; OP = outpatient study visit; [redacted] RR = respiratory rate; SAE = serious adverse event; SV = Screening Visit; W = week.

[a] Screening assessments may be completed in any reasonable order (except where indicated) and on more than 1 day at the Investigator's discretion. All screening assessments must be completed within the Screening Period before Day 0.

[b] [redacted] should be completed prior to invasive assessments being conducted.

[c] Subjects will complete the GSDIa Morning Diary and GSDIa Evening Diary daily for 7 days leading up to and including the Day 0 and 12, 24, and 52 study visits. Subjects will complete the GSDIa Morning Diary in the morning upon awakening. Subjects will complete the GSDIa Evening Diary at the end of the day. Subjects will be provided with copies of the GSDIa Morning Diary and GSDIa Evening Diary during the Screening Period and instructed to bring the completed assessments to each study inpatient visit.

[d] Subjects will be asked to complete a brief telephone interview at Weeks 24 and 52 regarding their experience completing the [redacted] assessments to guide further development of the assessments. At Week 52, subjects will also be asked about their experience in the study.

[e] Vital signs will be measured approximately 5 minutes after the start of the infusion, and approximately 0.5 (± 5 minutes), 1 (± 5 minutes), 4, 8 hours (± 15 minutes), and 22 hours (± 1 hour) after the start of infusion.

[f] Complete physical examination will include assessments of the head, eyes, ears, nose, and throat; the skin; the abdomen with documentation of liver and spleen size; and the endocrine, metabolic, neurological, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems.

[g] Targeted physical examination will include assessments of the skin; the abdomen with documentation of liver and spleen size; and the respiratory, cardiovascular, and gastrointestinal systems.

[h] It is recommended that the Screening sample for *G6PC* genotyping be collected at the time written informed consent is provided.

[i] Liver function tests will be assessed at a minimum of every 3 to 4 days starting at DTX401 post dose Day 4 through Week 12, or longer if clinically indicated. One blood sample will be collected for determination of clinical chemistry (including LFTs) and sent to the central laboratory for analysis. A second blood sample will be collected for determination of LFTs and sent to the local laboratory (STAT sample), as described in the laboratory manual.

[j] Liver function tests and triglyceride levels can be repeated during the Screening Period at the Investigator's discretion.

[k] A blood sample for measurement of lipid levels will be collected on the morning of hospital admission for each controlled fasting challenge at approximately the same time starting at Day 0. The sample should be collected at least 2 to 4 hours after the subject's last meal.

[l] A blood sample for determination of clinical chemistry (including LFTs) will be collected approximately 22 hours after the start of DTX401 infusion.

[m] Blood samples for measurement of cortisol, fatty acid, glucagon, insulin, C-peptide, growth hormone, IGFBP1, ACTH, alanine, and ketone levels will be collected at the beginning and end of each controlled fasting challenge, or more frequently at the Investigator's discretion.

[n] If possible, a blood sample for measurement of ACTH and cortisol levels will be collected approximately 1 week before the Week 12 visit.

[o] It is recommended that the Screening sample for AAV8 neutralizing antibody testing be collected at the time written informed consent is provided.

[p] A blood sample for vector genome determination will be collected approximately 22 hours after the start of DTX401 infusion.

[q] [redacted]

[r] The subject's daily prescribed diet and daily diet intake will be recorded at the time points specified in Table 6 and, if possible, on a weekly basis through the Week 52 visit or early withdrawal.

[s] The subject will remain on his or her prescribed diet for the duration of each inpatient study visit.

[t] The subject's daily prescribed cornstarch (or equivalent) and daily cornstarch (or equivalent) intake will be recorded at the time points specified in Table 6 and, if possible, on a weekly basis through the Week 52 visit or early withdrawal.

[u] Supplemental information on glucose level trends will be collected using a CGM device. The site will provide a CGM device to the subject during the Screening Period after determining that the subject is eligible for the study. Subjects will be educated on the appropriate care and use of the CGM device and sensors, and instructed to wear the CGM device through the Week 52 visit or early withdrawal. Data from the subject's CGM device will be transferred to the Sponsor throughout the study, including a final data transfer at the end of the Week 52 visit or early withdrawal.

[v] Subjects will receive the Morning Glucose Level monitoring worksheet and instructions for completing it following DTX401 administration. 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 and record the values on the Morning Glucose Level monitoring worksheet. Subjects should measure their morning glucose level using their own glucose monitoring device before taking their morning dose of cornstarch. Subjects will be instructed to bring the completed worksheet to each study visit.

[w] If the subject was unable to use the assigned CGM but was able to complete the Morning Glucose Level monitoring worksheet, the subject's worksheet will be collected and reviewed at the time points specified in Table 6, and a new worksheet will be provided to the subject.

[x] Before the controlled fasting challenge begins, the study site will provide dinner for the subject. The dinner meal will be personalized for each subject, and will include a target carbohydrate range and overall composition in protein, fats and dietary fibers that is as close as possible to the subject's most current dinner dietary prescription, but not higher than the carbohydrate content of the dinner consumed at their baseline fasting challenge.

[y] Subjects will be given an oral dose of cornstarch equivalent per their most recent cornstarch prescription at approximately the same time that they typically take it, but no later than 3 hours post dinner.

[z] The controlled fasting challenge requires a 24-hour inpatient stay and should be performed after all other assessments are completed except for 24-hour urine collection, which may be completed concurrently, and [redacted] which will be completed after the controlled fasting challenge. In addition to the specified time points, if clinically indicated, the controlled fasting challenge can be performed at an unscheduled visit.

[aa] Blood samples for measurement of glucose and lactate (venous) levels will be collected at the beginning of the controlled fasting challenge, then approximately every 60 minutes (± 5 minutes) until the glucose level decreases to ≤ 70 mg/dL (≤ 3.9 mmol/L), then approximately every 30 minutes (± 5 minutes) until the glucose level decreases to < 54 mg/dL (< 3.0 mmol/L) or the fast reaches 15 hours without hypoglycemia, whichever occurs first. Samples should be sent to the local laboratory (STAT sample) and results should be available within 30 minutes or less of blood sample collection for the safety of the subject.

[bb] Subjects will be registered in the IWRS at Screening and after eligibility for enrollment is confirmed.

[cc] The site will schedule the dosing visit in the IWRS no less than 3 days before, preferably 7 days before, the DTX401 infusion to allow time for DTX401 to be shipped and delivered to the site.

[dd] If the subject continues to be on steroid regimen and the Investigator determines that it is not safe to proceed with the CFC, the Week 12 visit may become an outpatient visit. Investigators should try to complete an adhoc CFC assessment as soon as the subject has completed steroid treatment and within 8 weeks of the Week 12 visit, as an unscheduled visit.

15.2. Appendix 2: Continual Reassessment Method Details

The nominal doses used in the continual reassessment method, the x-hats, will be derived as:

$$\hat{x}_i = \log\left(\frac{d_i}{d_{ref}}\right)$$

Where $d_1 = 2$, $d_2 = 6$, $d_3 = 10$ and $d_{ref} = 6$. The d_i correspond to the amount of DTX401 administered at each dose level, in units of 10^{12} genome copies/kg.

A logistic model will be used to model the dose-toxicity curve. Let

$$Y_i = \begin{cases} 0 \; if \; the \; ith \; subject \; does \; not \; experience \; a \; DLT \\ 1 \; otherwise \end{cases}$$

Then

$$p(Y = 1|\hat{x}_i, \alpha, \beta) = \frac{e^{\alpha+\beta\hat{x}_i}}{1 + e^{\alpha+\beta\hat{x}_i}}$$

The joint distribution of α and β is given by

$$\begin{pmatrix} \alpha \\ \log\beta \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_\alpha \\ \mu_\beta \end{pmatrix}, \begin{pmatrix} \sigma_\alpha \times \sigma_\alpha & \sigma_\alpha \times \sigma_\beta \times \rho \\ \sigma_\alpha \times \sigma_\beta \times \rho & \sigma_\beta \times \sigma_\beta \end{pmatrix}\right)$$

Initial (prior) values $\mu_\alpha = -2.3097$, $\log\mu_\beta = -0.4323$, $\sigma_\alpha = 1.6604$, $\log\sigma_\beta = 0.0044$ and $\rho = -0.2405$ are used based on simulations.

The estimate of the maximum tolerated dose will be the highest dose for which the full Bayes posterior estimate of $p(DLT|d_i)$ is strictly less than or equal to the target toxicity rate.

A dose is cleared if it is either 2×10^{12} genome copies/kg or if it is no more than 1 dose level higher than the highest dose at which at least 3 subjects have been treated.

15.3. Appendix 3: [redacted]

[redacted]

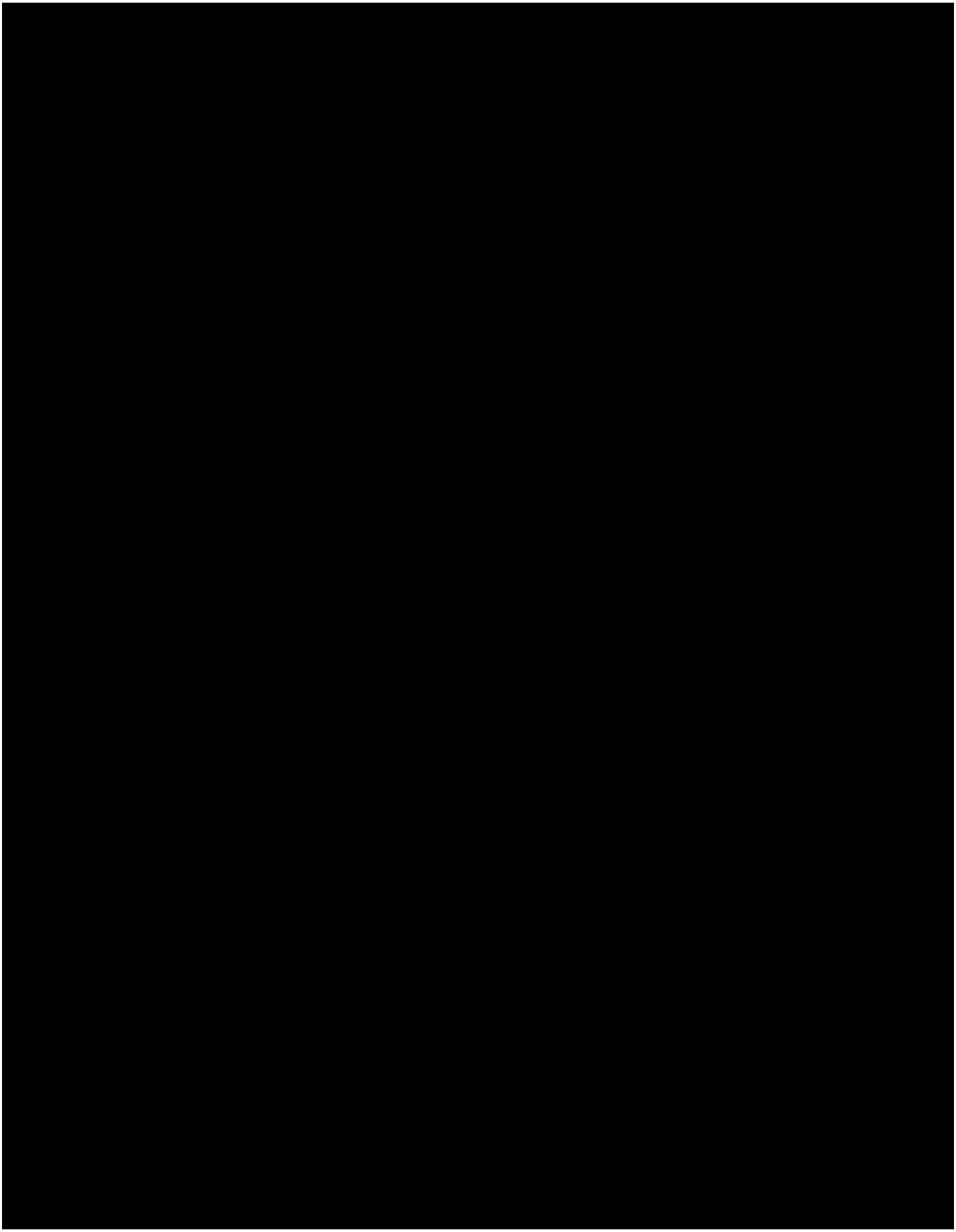
Please respond to each question or statement by marking one box per row.

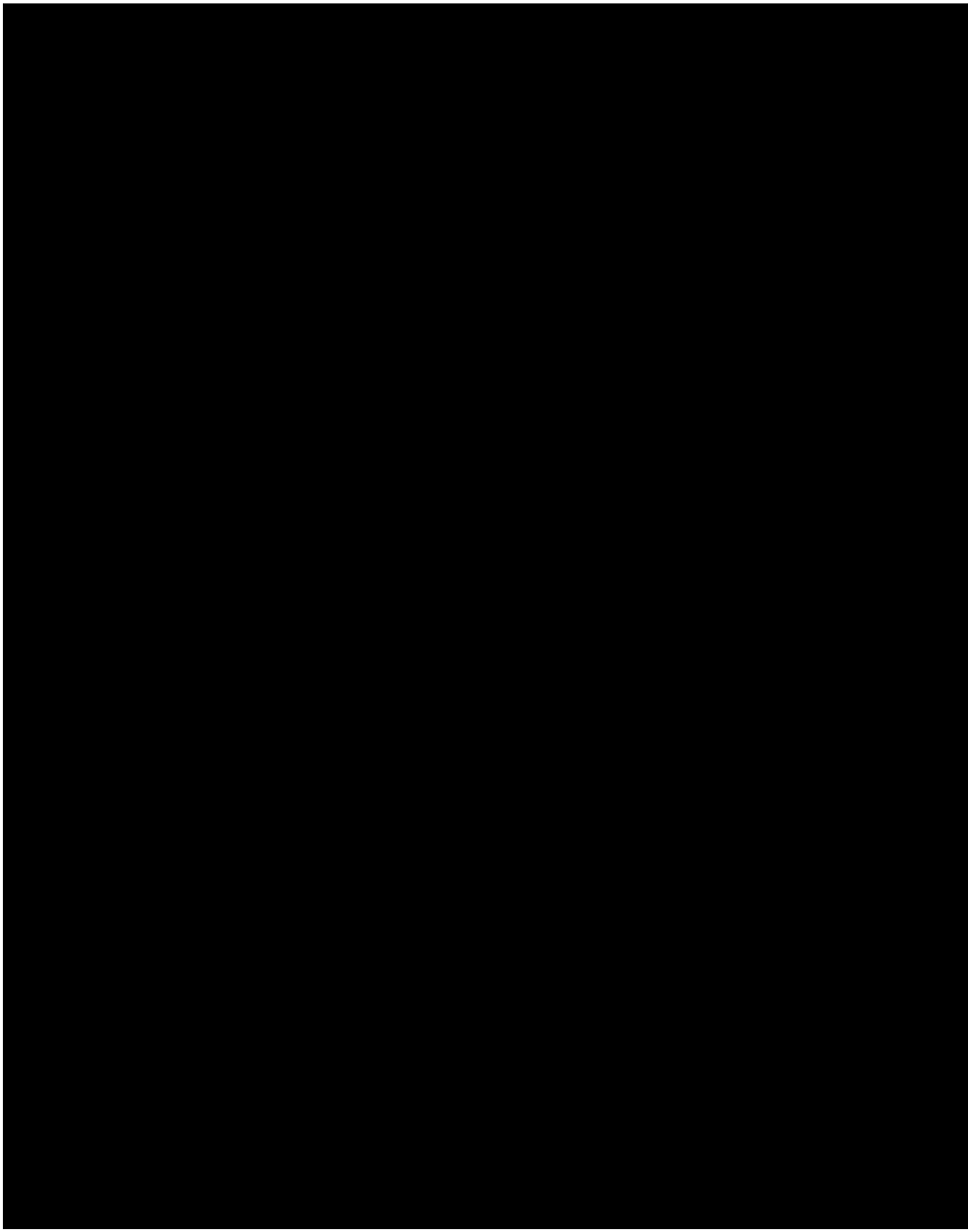
[redacted]

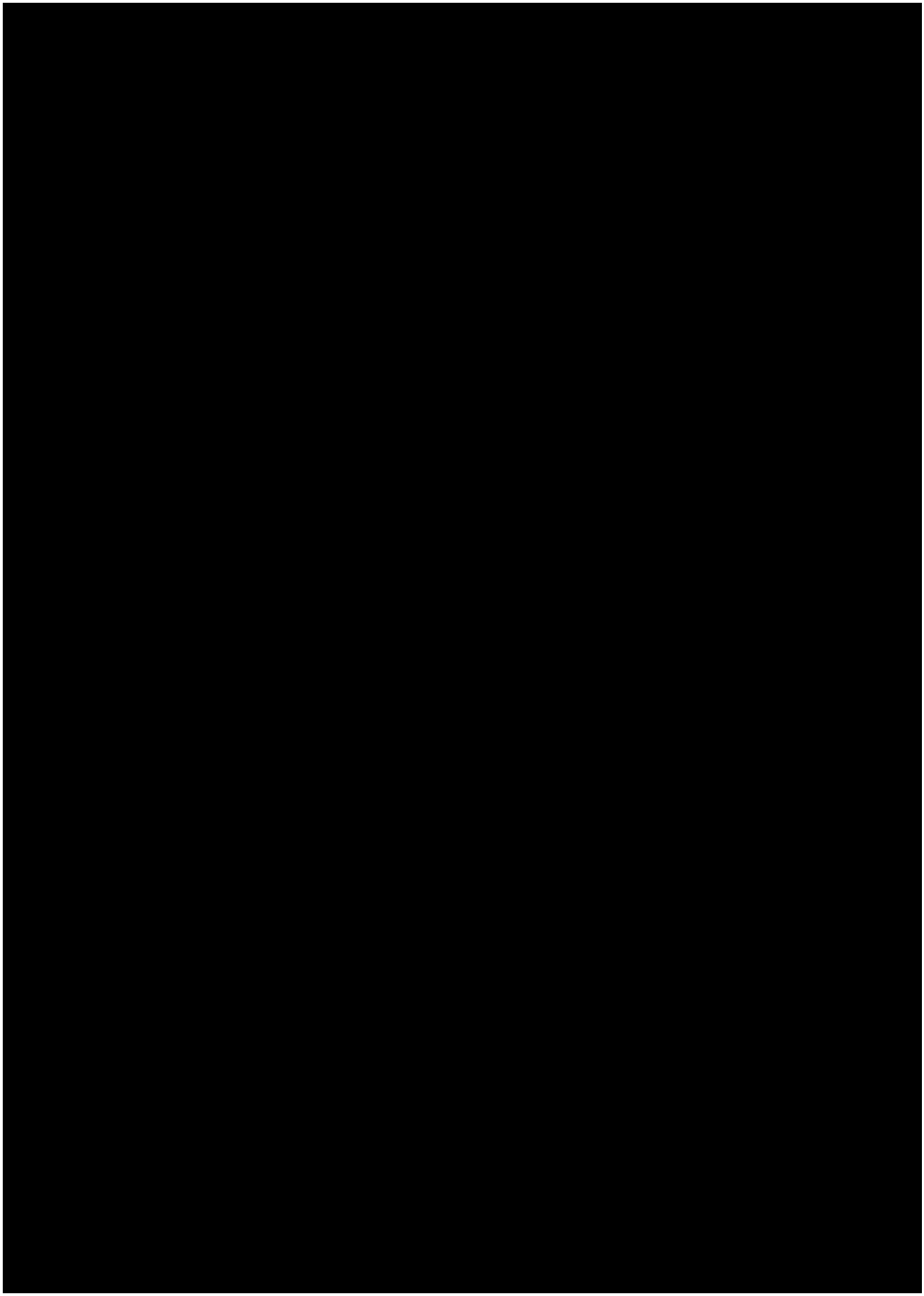
[redacted]

15.4. Appendix 4: [redacted]

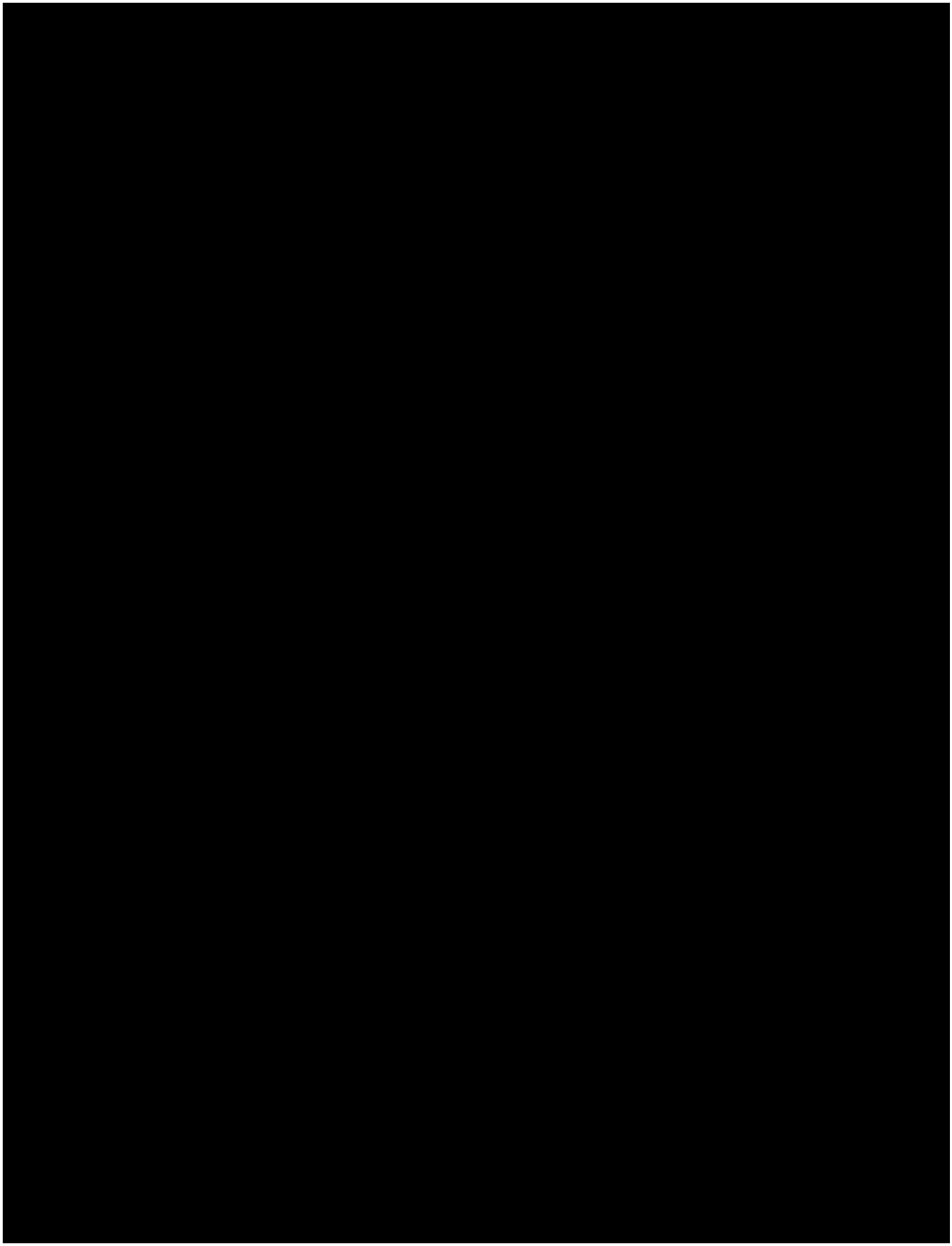
[redacted]



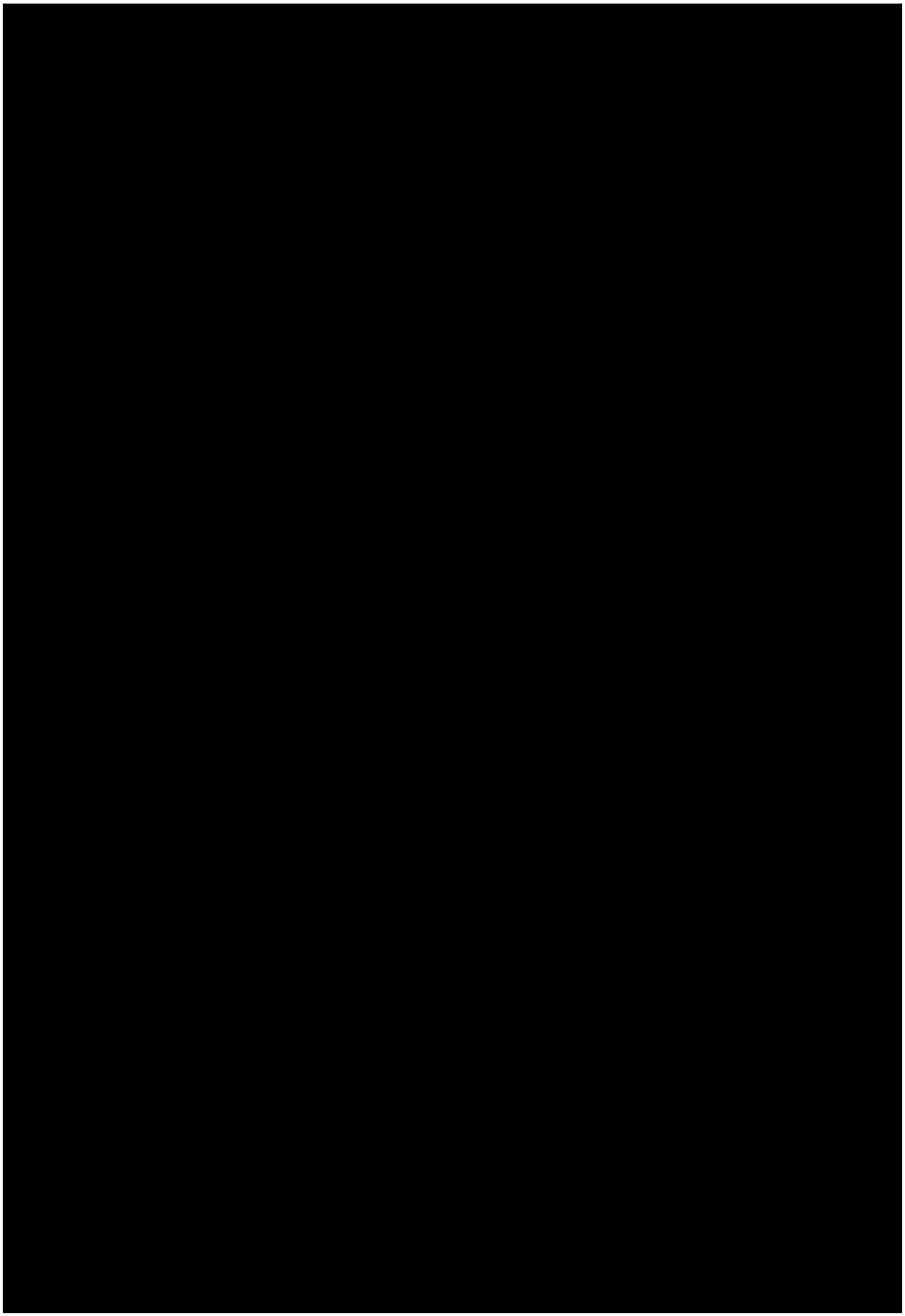


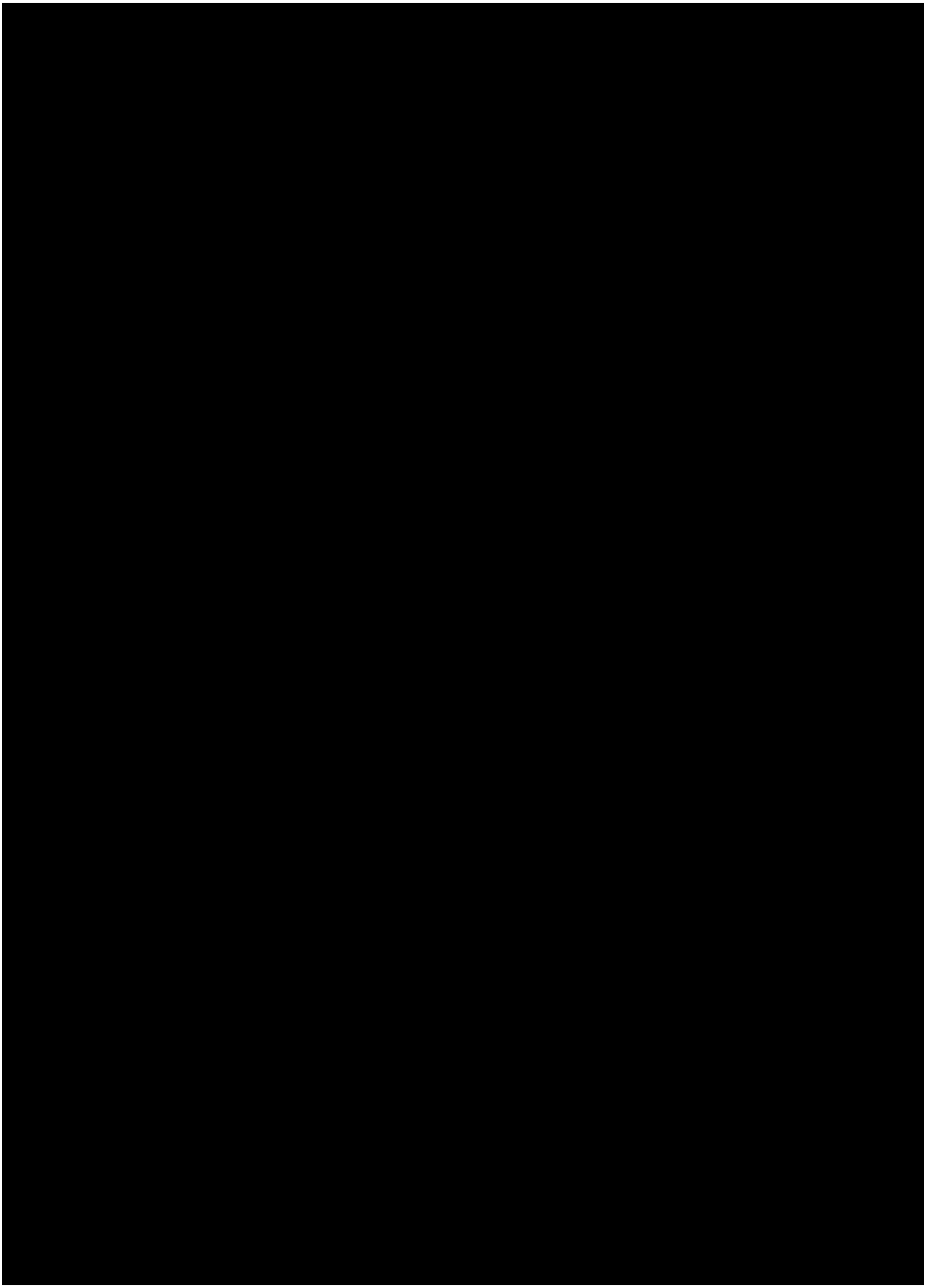


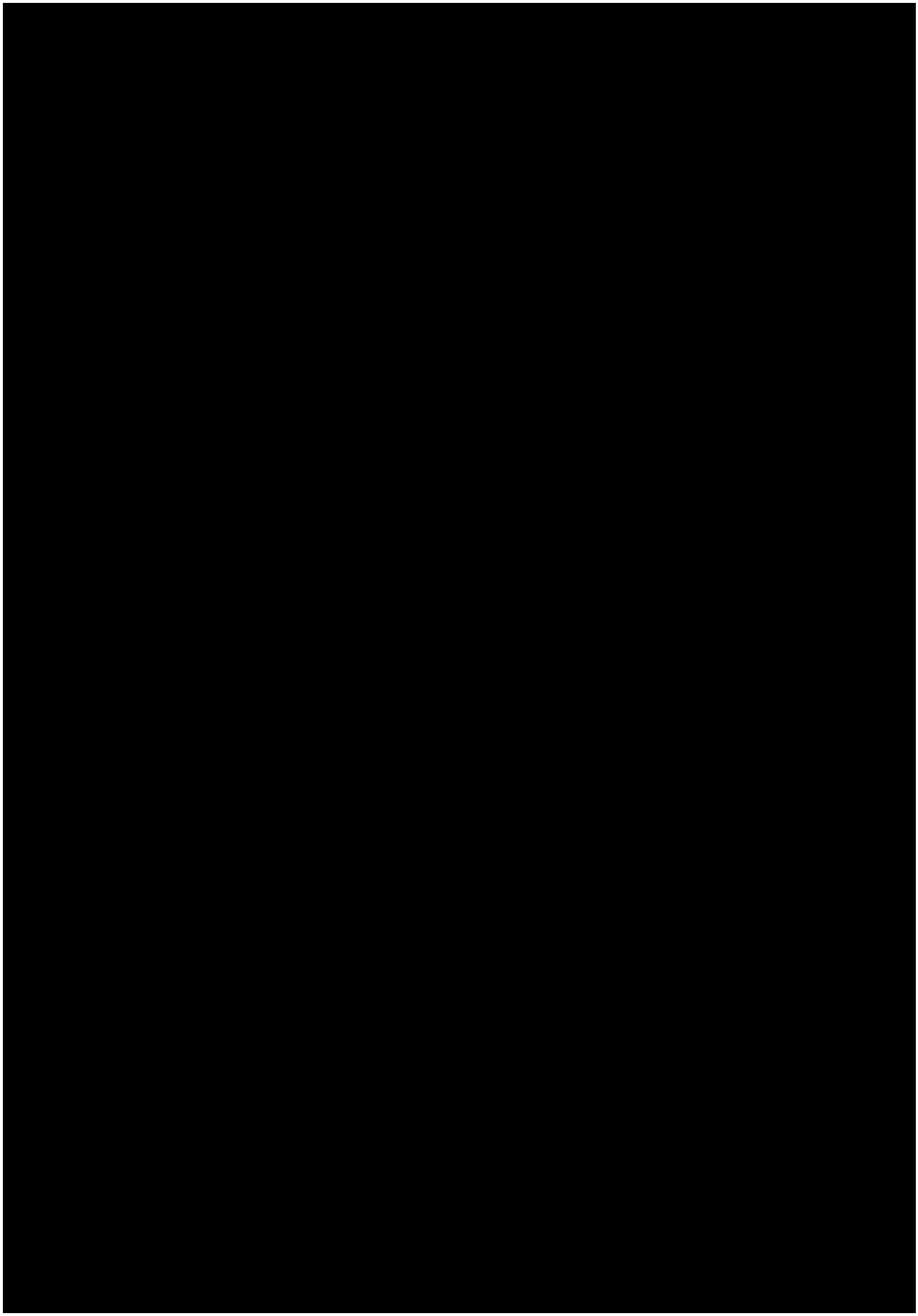
15.6. Appendix 6: Glycogen Storage Disease Type Ia (GSDIa) Morning Diary

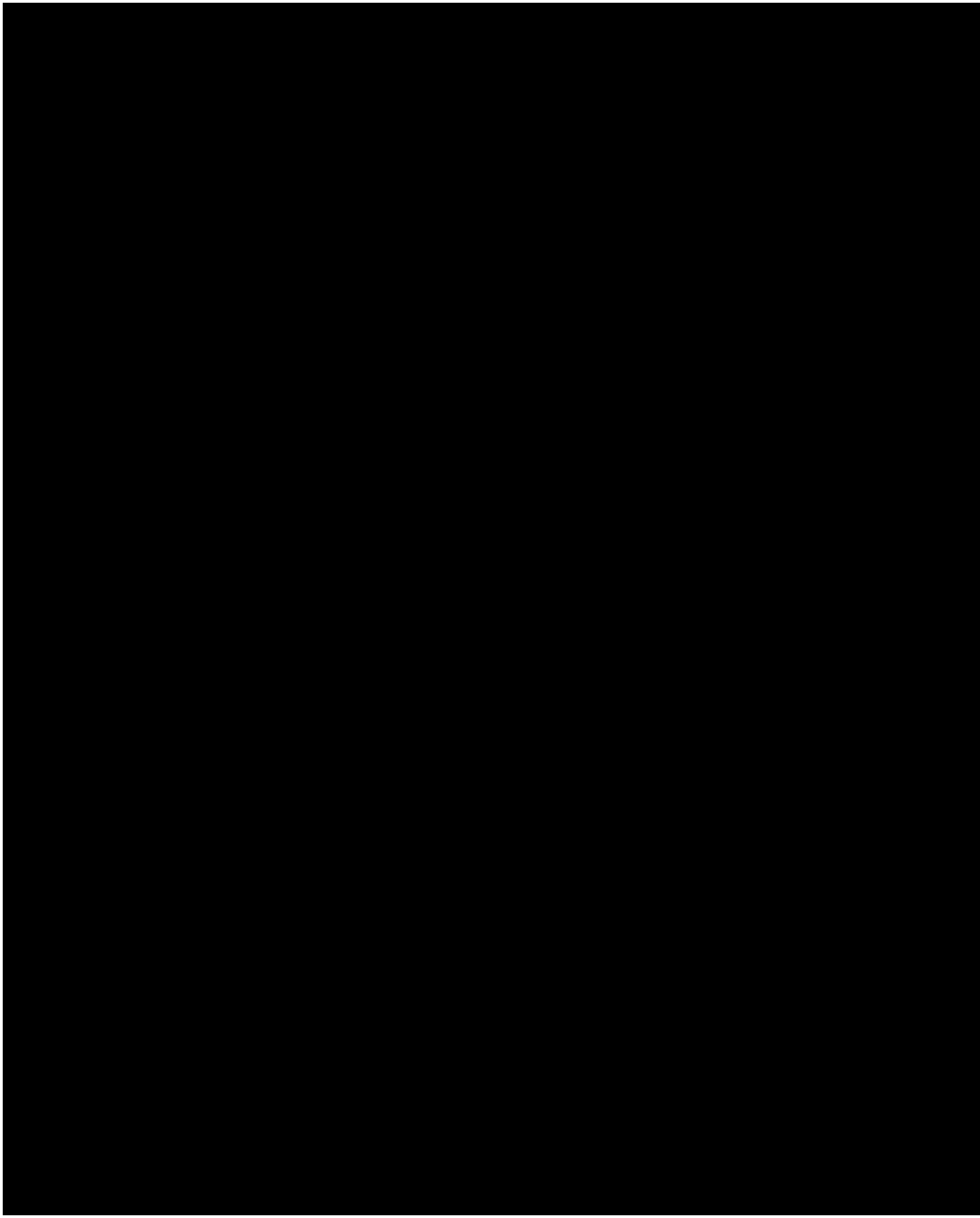


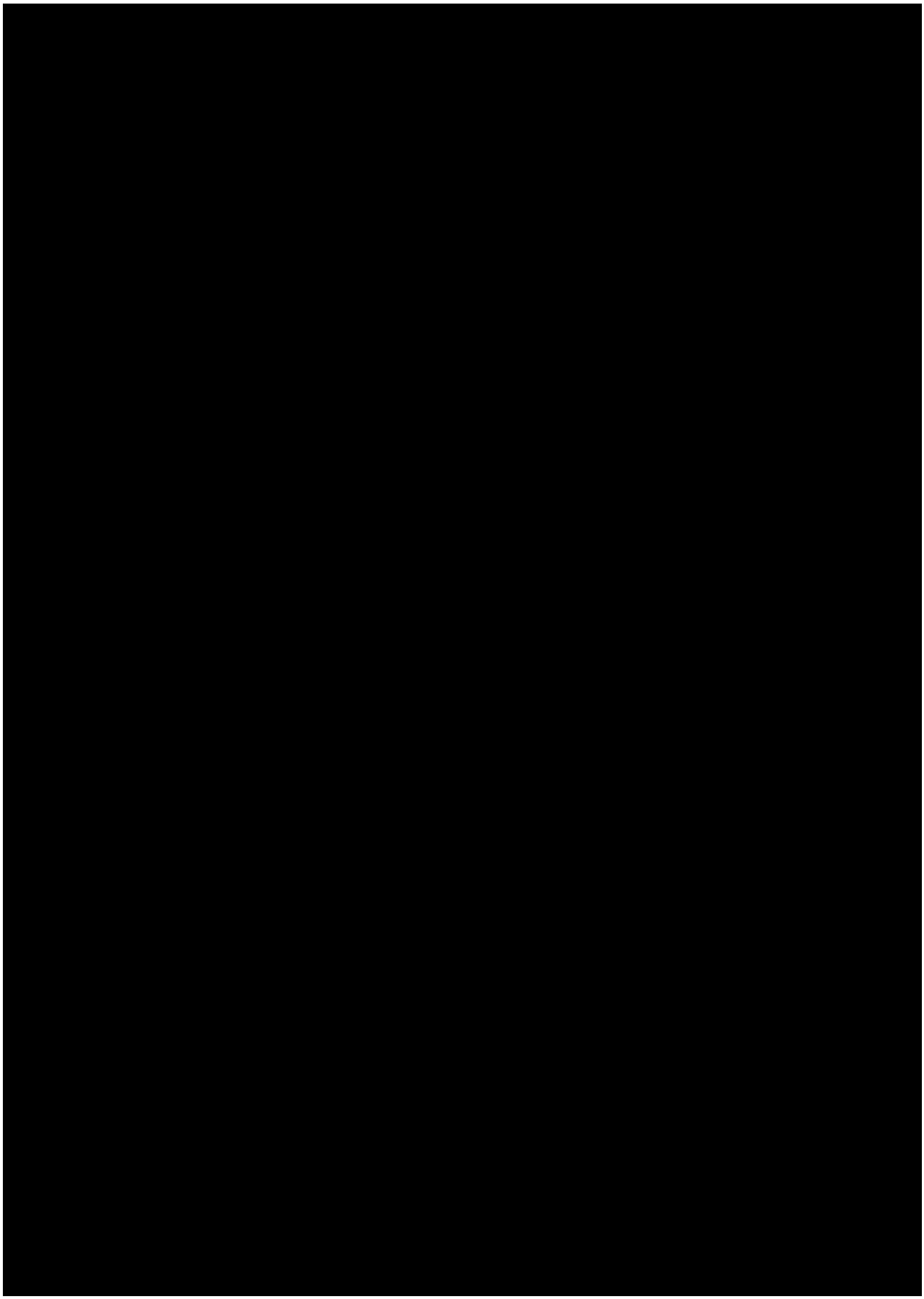
15.7. Appendix 7: Glycogen Storage Disease Type Ia (GSDIa) Evening Diary



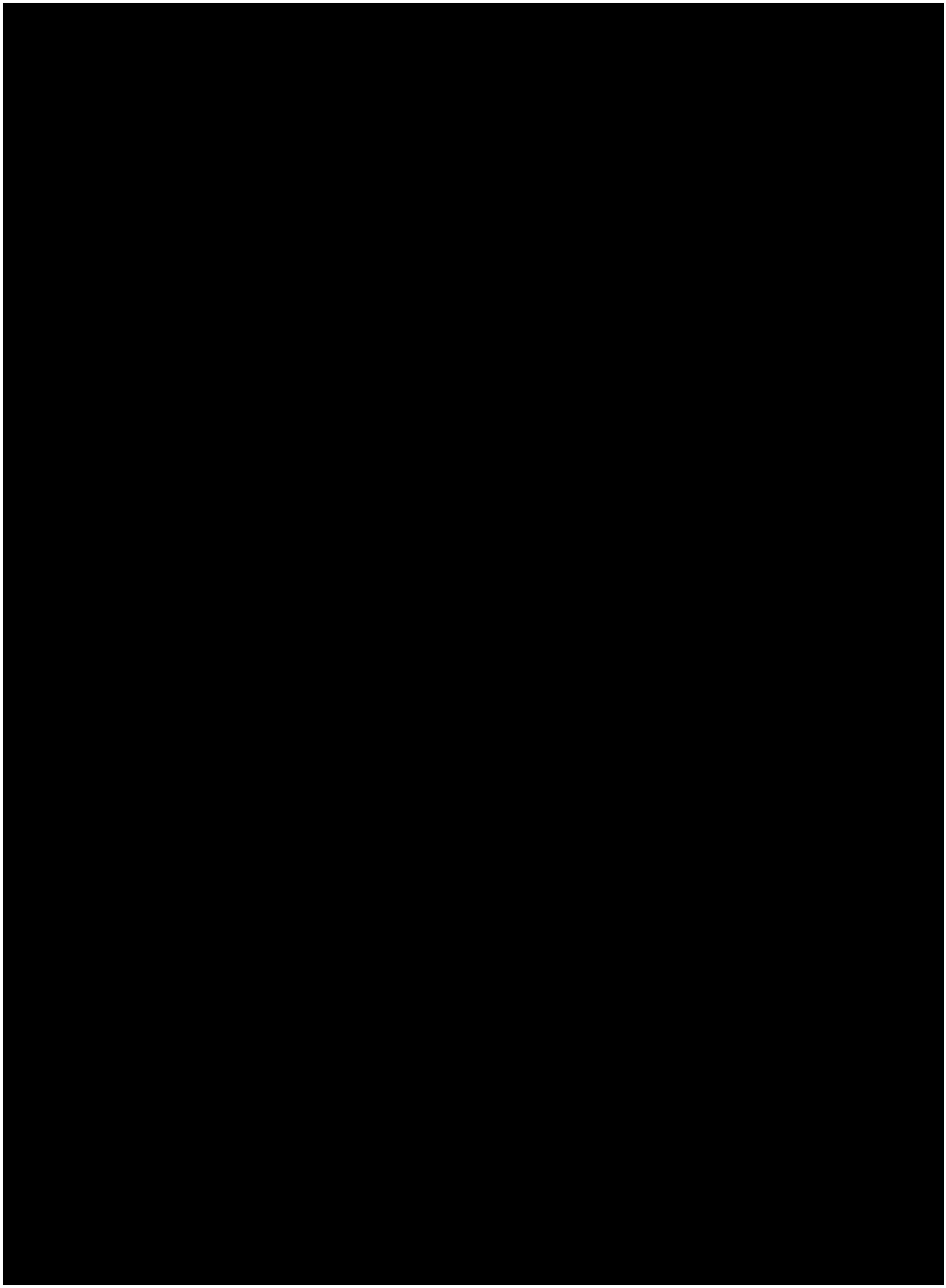








15.8. Appendix 8: [redacted]



15.9. Appendix 9: [redacted]