A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Adeno-associated Virus Serotype 8-mediated Gene Transfer of Glucose-6-phosphatase in Patients With Glycogen Storage Disease Type Ia

Protocol Number: DTX401-CL301

Original Protocol: 11 February 2021
Amendment 1: Global Amendment 08 July 2021
Amendment 2: Global Amendment 24 February 2023
Amendment 3: Global Amendment 06 July 2023

Product number:	DTX401 (pariglasgene brecaparvovec)
Indication:	Glycogen storage disease type Ia
IND Number:	17965
EudraCT Number:	2020-004184-12
Sponsor:	Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949 USA
Sponsor's Responsible Medical Lead:	PPD Ultragenyx Pharmaceutical Inc. Telephone: PPD Email: PPD

This study will be performed in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES AND RATIONALE

Protocol DTX401-CL301 Amendment 2 dated 24 February 2023 has been modified by Amendment 3. Previous amendments are summarized in Appendix 8.

This amendment is considered to be substantial. Minor edits and typographical corrections have also been made. Changes impacting study design and/or conduct are summarized below. In addition to the sections described below where changes occurred, relevant updates were made to the Synopsis.

Section # and Name	Description of Change	Brief Rationale
Schedule of Events, Table 5 Section 7.2.1 Duration of Subject Participation	Added Year 3 of follow-up	Collection of additional safety and efficacy data in subjects prior to enrollment in the Disease Monitoring Program.
Schedule of Events, Table 3 and Table 4 Section 7.1.2 Cornstarch Modification Guidance Section 10, Assessments	• Weeks 4, 6, 12 visits in Year 1 and Weeks 52, 54, 60 visits in Year 2 were changed from outpatient to outpatient or home health visits • Week 24 visit in Year 1 and Week 72 visit in Year 2 were changed from inpatient to outpatient or home health • Weeks 30, 42 visits in Year 1 and Weeks 78, 90 visits in Year 2 were changed from outpatient or home health to phone calls; assessment of weight, vital signs, standard clinical chemistry panel and urine pregnancy test were removed • Visit windows were increased from +/-7 to +/-14 days for certain visits in Year 1 and 2 • Added footnote text reducing liver function test assessment at Weeks 4-11 in Year 1 and Weeks 52 – 59 in Year 2 from weekly to every two weeks if test results are stable and per investigators discretion • EQ-5D-5L/EQ-5D-Y assessment removed from Week 24 in Year 1 and Week 72 in Year 2	Burden has been reported in the study due to challenges experienced by subjects with study participation. A number of changes have been made to the schedule of events to reduce burden of assessments for subjects. These changes were paramount in improving subject experience and reducing the risk of subject attrition in the study.

Section # and Name	Description of Change	Brief Rationale
	• Removed urinalysis assessment from Weeks 4 and 6 of Year 1 and Weeks 52 and 54 of Year 2 • 24-hour urine collection removed from Week 24 and Week 36 in Year 1, and Week 72 and Week 84 in Year 2 • HEOR assessments removed from Weeks 24 and 72, and added to Weeks 36 and 84 • Reduced frequency of SMBG to 4 times a day for 1 week prior to visits at Weeks 24, 30, 36, 42 and 48 in Year 1 and Weeks 72, 78, 84, 90 and 96 in Year 2. Additional SMBG assessments to be performed per Investigator's discretion or if symptomatic • Recording of cornstarch intake was reduced to at least 1 week prior to visits at Weeks 24, 30, 36 and 42 in Year 1 and Weeks 72, 78, 84 and 90 in Year 2 • Recording of diet diary was reduced from 7 consecutive days to 3 consecutive days • SMBG diary entries required only if the subject is symptomatic • Removed GSD FAD assessment from Week 24, Week 72 and Early Withdrawal visits	
Section 5.2.3 Previous Clinical Studies	Included a summary of safety data for Studies 401GSDIA01 and 401GSDIA02 as of 19 April 2023.	Updated safety data available
Section 5.4 Potential Risks and Benefits	• Infusion-related reactions added as an important potential risk and adverse event of special interest (AESI) • Adrenal insufficiency is considered a potential risk of study-related procedures and is an AESI.	IRRs with features of hypersensitivity have been observed with blinded IP in this trial. Events of adrenal insufficiency attributed to prednisolone/placebo administration were observed in this trial.

Section # and Name	Description of Change	Brief Rationale
Section 5.5, Risk Minimization	To minimize burden of clinical study participation on subject's mental well-being, independent psychosocial support may be considered by subject's at their own discretion and reimbursed by the Sponsor in accordance with the ICF	Ultragenyx recognizes, based on feedback from PIs and subjects, clinical study participation can be burdensome to subjects.
Section 5.5, Risk Minimization Section 9.2 Prednisolone Taper Schedule of Events, Table 3 and Table 4	• Investigators will educate subjects on risks of prednisolone and the importance in adherence to the prednisolone/placebo regimen and reporting of any undesirable effects. • Investigators will call subjects during steroid tapering regimen to evaluate signs of iatrogenic Cushing's syndrome and adrenal insufficiency. • An early morning cortisol and ACTH should be obtained 24 hours after completing the prednisolone/placebo taper, and any abnormal levels should be reviewed by the CIC	Risk minimization approach updated for increased subject safety
Section 5.5, Risk Minimization Section 9.1.3, Preparation and Administration Section 9.1.4, Clinical Observation and Supportive Care Schedule of Events, Table 3 and Table 4	• Premedication including acetaminophen/paracetamol, 2nd generation H1 antagonist and H2 antagonist to be administered 30 to 60 min prior to start of dosing. • Blinded IP to be administered slowly per infusion rates specified in Pharmacy Manual	Minimize risk of infusion-related reactions including hypersensitivity to ensure subject safety
Section 6, Objectives and Endpoints	• Secondary endpoints updated to remove "based on SMBG data collected during the 1 week prior to the visit" • Removed noninferiority margins for secondary endpoints for glycemic control • Removed the following tertiary endpoint: Percentage of glucose values in the range of 70-120 mg/dL [3.9-6.7 mmol/L] based on CGM data	Both SMBG and CGM will be used to evaluate the endpoint and details of analyses will be included in the SAP. Non-inferiority margins will be specified in the SAP. Percentage of glucose values in the range of 70-120 mg/dL will be analyzed by both SMBG and CGM as part of secondary endpoint analysis,

Section # and Name	Description of Change	Brief Rationale
	• Added the following tertiary endpoint: PGIC-CTT assessment score at Week 48	and therefore the tertiary endpoint based on CGM was removed PGIC-CTT assessment score included to capture the patient perspective of changes in gastrointestinal symptoms associated with cornstarch use since the start of the study
Section 7.1.1, Study Periods Section 9.2.1, Vaccination and Oral Prednisolone Regimen	Updates made to indicate the administration of IP will be delayed if a subject has had any vaccination, infection (febrile or nonfebrile) or disease flare within 1 month of scheduled IP administration	Minimize risk of adverse events
Section 7.1.1, Study Periods	Frequency of holding visits changed from every 6 weeks to every 12 weeks	Minimize subject burden
Study Interventions, Table 12	Included premedication to be administered prior to dosing	Premedication to be administered to minimize risk of infusion-related reactions including hypersensitivity to ensure subject safety
Section 9.1.4, Clinical Observation and Supportive Care	Included use of a pulse oximeter for the full duration of the infusion	To monitor O2 saturation
Section 9.1.4, Clinical Observation and Supportive Care Infusion Instructions for Adverse Reactions, Table 13	Infusion to be paused immediately if any symptoms or signs of an infusion-related reaction are observed Included conditions under which infusion may be resumed	To minimize potential risks and ensure subject safety
Section 10 Assessments	To minimize burden of clinical study participation on subject's mental well-being, independent psychosocial support may be considered by subject’s at their own discretion and reimbursed by the Sponsor in accordance with the ICF	Ultragenyx recognizes, based on feedback from PIs and subjects, clinical study participation can be burdensome to subjects.

Section # and Name	Description of Change	Brief Rationale
Section 10.1 Data Collection Devices Provided to Subjects	Paper format may be used if eDiary is unavailable or not in use	To provide an alternative option to capture cornstarch and dietary intake in case eDiary is not available
Section 10.2.2, Capillary Blood Glucose Monitoring Schedule of Events, Table 3 and Table 4	Reduced frequency of SMBG to be per Investigators discretion and if symptomatic	Reduce burden of assessments for subjects
Section 10.2.4, Controlled Fasting Challenge Schedule of Events, Table 3 and Table 4	Removed controlled fasting challenge assessment from Week 24 of Year 1 and Week 72 of Year 2	Removal of CFCs at Week 24 and 72 to reduce the burden associated with inpatient visits at these timepoints. The impact of this change on analysis of the CFC related secondary efficacy endpoint is expected to be minimal. Sensitivity analysis will be performed to assess the impact (if any) and this analysis will be described in the Statistical Analysis Plan.
Section 10.2.5 Glycogen Storage Disease Functional Assessment Diary Schedule of Events, Table 3 and Table 4	Included a paper-based, weekly version of the GSD FAD that applies a 7-day recall to the items at Week 48 and Week 96 visits	To evaluate the equivalence of the daily eDiary GSD FAD and the weekly GSD FAD
Section 10.2.6 Patient Global Impression of Change and Patient Global Impression of Severity Measures Schedule of Events, Table 3 and Table 4 and Table 5	Relevant updates made to include Patient Global Impression of Cornstarch Treatment Tolerance (PGIC-CTT)	To capture the patient perspective of changes in gastrointestinal symptoms associated with cornstarch use since the start of the study
Section 10.5.5, Complement Assessments Schedule of Events, Table 3 and Table 4	Included assessment of complement activity (C3, C4, SC5b-9, CH50, AH50, MBL) prior to dosing with blinded IP and post-dose in subjects with infusion-related reactions	To assess mechanism of action of infusion-related reactions
Section 10.5.6, Serum Tryptase Assessment Schedule of Events, Table 3 and Table 4	Included assessment of serum tryptase prior to dosing with blinded IP and post-dose in subjects with infusion-related reactions	To assess baseline tryptase values

2. SYNOPSIS

Sponsor: Ultragenyx Pharmaceutical Inc. (Ultragenyx)

Ultragenyx Product: DTX401 (pariglasgene brecaparvovec)

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Adeno-associated Virus Serotype 8-mediated Gene Transfer of Glucose-6-phosphatase in Patients With Glycogen Storage Disease Type Ia

Development Phase: Phase 3

Introduction:

DTX401 is a gene therapy that is being developed for the treatment of glycogen storage disease type Ia (GSDIa). Study DTX401-CL301 is a pivotal study to determine the efficacy and safety of DTX401 in pediatric (8 to < 18 years) and adult (≥ 18 years) patients with GSDIa.

Objectives and Endpoints:

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of DTX401 to reduce or eliminate dependence on exogenous glucose replacement therapy needed to maintain glucose control	• Percent change from Baseline to Week 48 in daily cornstarch intake for the DTX401 Group compared with the Placebo Group
Secondary (subject to multiplicity)	
To evaluate the effect of DTX401 on reducing the frequency of exogenous glucose replacement therapy	• Change from Baseline to Week 48 in number of total daily doses of cornstarch
To evaluate the effect of DTX401 on glucose control	• Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (<70 mg/dL [3.9 mmol/L]), assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority.
To evaluate the effect of DTX401 on subject experience of disease	• PGIC assessment score at Week 48
Secondary (not subject to multiplicity)	
To evaluate the effect of DTX401 on glucose control	• Change from Baseline to Week 48 in time to hypoglycemia (<54 mg/dL [3.0 mmol/L]) during the CFC • Change from Baseline to Week 48 in percentage of glucose values in the range of 70-120 mg/dL (3.9-6.7 mmol/L), assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority

Objectives	Endpoints
To evaluate the safety of DTX401	• Incidence, severity, and relationship to investigational product of TEAEs, TEAEs of special interest, serious TEAEs, related TEAEs, discontinuations from study or investigational product due to AEs, and fatal AEs

AE, adverse event; CFC, controlled fasting challenge; PGIC, Patients Global Impression of Change; SAP, Statistical Analysis Plan; SMBG, self-monitoring blood glucose; TEAE, treatment-emergent adverse event

Study Design:

Study DTX401-CL301 is a Phase 3, randomized, double-blind, placebo-controlled study to determine the efficacy and confirm the safety of DTX401 in patients 8 years and older with GSDIa. Approximately 50 subjects will be enrolled and randomly assigned in a 1:1 ratio to receive DTX401 (n = 25) or placebo (n = 25). Approximately 20 subjects 8 to < 18 years of age will be enrolled. Randomization will be stratified by age (< 18 years vs ≥ 18 years) and baseline percentage of values in the target blood glucose range (< 60%, ≥ 60% and ≤ 85%, > 85%).

This study includes the following sequential stages:

- **Screening (Day -122 to Day -10):** The site must obtain written informed consent for participation in the study before performing any study-specific screening tests or evaluations. (For pediatric subjects, a legal guardian must provide written informed consent, and the subject must provide age-appropriate assent to participate.) Section 8.5 provides additional details regarding subject consent/assent.

  All screening evaluations specified in Table 3 must be completed by the Investigator and reviewed to confirm that subjects meet all eligibility criteria.

  The subject/caregiver should be given the continuous glucose monitoring (CGM) system, a meter for capillary glucose measurements (ie, self-monitored blood glucose [SMBG]), and the electronic diary (eDiary) to start collecting baseline data immediately after signing the informed consent form (ICF; unless deemed ineligible by that time). Section 10.2.2 and Section 10.2.3 provide additional details.

  The Screening Period will be up to 112 days (16 weeks), depending on the duration of time needed to establish glycemic and cornstarch stability according to the following considerations:

  After the first week of screening, the Investigator and/or study dietitian will review the subject's current diet, cornstarch regimen, and glycemic control (assessed by both CGM and SMBG measurements) to determine if the subject requires nutrition modifications or if the subject's diet, cornstarch, and glycemic control are considered optimized (see "Nutrition Optimization Period" below). Nutritional management should be consistent with published guidelines (see Appendix 1 and Study Reference Manual). If a subject does not require nutrition optimization, they may begin the 4-week stabilization period immediately.

  – **Nutrition Optimization Period:** The goal of nutrition optimization is to adjust cornstarch dosing and diet to minimize the occurrence of hypoglycemia and minimize elevations in lactate, triglycerides, and uric acid, while avoiding excessive cornstarch consumption, which can lead to obesity, hyperlipidemia,

worsening hepatomegaly, and metabolic instability caused by hyperinsulinemia and rebound hypoglycemia. Nutrition education and close monitoring of diet, cornstarch, and glycemic control will be provided according to nutritional guidelines (see Appendix 1). Once the Investigator and/or dietitian determine the subject has achieved nutritional optimization, the subject will begin the nutrition stabilization period.

- **Nutrition Stabilization Period:** All subjects must demonstrate at least 4 consecutive weeks of glycemic, diet, and cornstarch stability prior to randomization.
  - Glycemic stability is achieved if the percentage of values in the target blood glucose range (60-120 mg/dL) each week for the most recent 4 weeks is within 15 percentage points of the average of each of the 4 weeks as measured by CGM and corroborated by SMBG. If adequate corroboration between CGM and SMBG is not observed, SMBG should be used for assessment of glycemic stability.
  - Cornstarch stability is achieved if the average daily cornstarch intake each week for the most recent 4 weeks is within 10% of the average of each of the 4 weeks.
  - Diet (non-cornstarch carbohydrate) stability will be achieved if average grams of non-cornstarch carbohydrates from food and beverage each week for the most recent 4 weeks is within 25% of the average of each of the 4 weeks.

Subjects will have up to 16 weeks from informed consent to complete nutrition optimization and stabilization.

The administration of IP will be delayed if a subject has had any vaccination, infection (febrile or nonfebrile) or disease flare within 1 month of scheduled IP administration.

- **Randomization Period (Day –10 to Day 0):** Screening ends when the subject is randomized. Using the interactive response technology (IRT) system, the site will randomly assign the subject to DTX401 or placebo treatment and schedule the investigational product (IP; ie, DTX401 or placebo) infusion at least 10 business days before the IP infusion date to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site. Investigators, site staff, subjects, and the Sponsor will be blinded to IRT treatment assignment. Once randomized, site staff must call the subject to complete assessments indicated in Table 3. During the period between Randomization and Baseline (Day 0), subjects must maintain cornstarch, diet, and glycemic stability. If cornstarch, diet, or glycemic stability is lost during this period, the Baseline visit may be postponed (after discussion with the Sponsor and Medical Monitor) or the subject may be withdrawn from the study. Medical monitor approval is required to proceed to the Baseline visit.
- **Baseline (Day 0):** The day before IP administration (ie, Day 0), the subject will be admitted to the hospital or a research facility for baseline assessments as specified in Table 3.

- **Day 1 IP Administration:** On Day 1, subjects randomly assigned to DTX401 will receive a single, blinded, peripheral IV infusion of DTX401 at 1.0×10^{13} genome copies (GC)/kg. Subjects randomly assigned to placebo will receive a single, blinded, peripheral IV infusion of normal saline (Section 9.1.3).
- **Day 15:** Subjects randomly assigned to DTX401 will start an oral prophylactic prednisolone regimen to minimize or prevent potential vector-induced hepatic effects (eg, transaminase elevations). Subjects randomly assigned to placebo IP infusion will receive a matching oral placebo regimen to maintain the study blind. Site staff must call the subject to complete assessments indicated in Table 3 and remind them to initiate the prophylactic regimen.
- **The Primary Efficacy Analysis Period (PEAP; Day 1 to Week 48):** The PEAP is the time from Day 1 post-dose through the completion of the Week 48 controlled fasting challenge (CFC). The primary endpoint and secondary efficacy endpoints will be analyzed after the last enrolled subject completes the Week 48 assessments.
- **Week 48 IP Preparation:** Before scheduling the IP administration at Week 48, the Investigator should review all results from the Week 36 assessments as soon as they are available and assess the subject according to Study Continuation Criteria (Section 8.3) to confirm that the subject is able to receive IP administration at Week 48. If there is evidence of any other change from Baseline in disease status or overall well-being that would preclude safe administration of DTX401 at Week 48, the Medical Monitor should be consulted. The administration of IP will be delayed if a subject has had any vaccination, infection (febrile or nonfebrile) or disease flare within 1 month of scheduled IP administration.
    - It is possible that a subject who received placebo at Day 1 may not be able to receive DTX401 at Week 48 due to development of anti-AAV8 antibodies or due to another postbaseline change in disease status or overall health. In this case, the subject and the Investigator will be notified during the Week 48 Visit and the subject will withdraw from the study once all Week 48 assessments are completed.
    - The Week 48 IP administration must be scheduled in the IRT system at least 10 business days before the IP infusion date to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site.
- **Week 48 IP Administration:** At Week 48, after all Week 48 assessments are completed, subjects will receive a second blinded infusion of IP. Subjects randomly assigned to DTX401 at Baseline will receive placebo at Week 48, while eligible subjects randomly assigned to placebo at Baseline will receive a single, blinded, peripheral IV infusion of DTX401 at 1.0×10^{13} GC/kg at Week 48 (if still eligible for IP infusion; see Section 8, Population).

  Refer to Section 9.1.3 for additional details regarding IP administration.

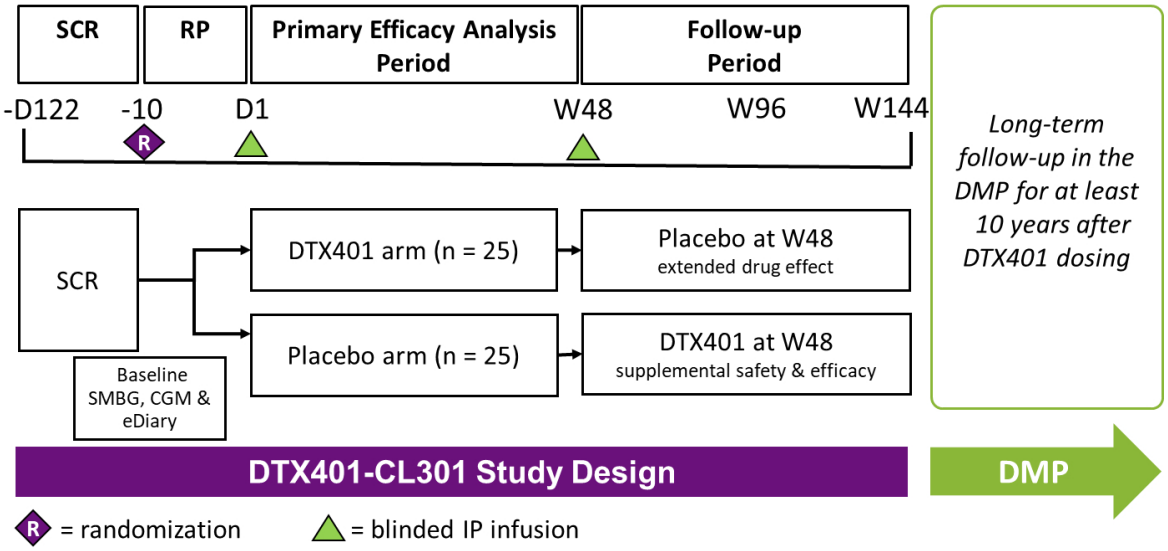
  Subjects will begin an oral prophylactic prednisolone regimen or matching oral placebo regimen (Section 9.2) 14 days after the Week 48 IP administration.

- **Holding Period (if required):** All Week 48 assessments must be complete prior to a subject entering into a Holding Period. The holding period consists of clinical or home health visits every 12 weeks as needed to allow continued follow-up of subjects following the PEAP (eg, in the event of an interruption to IP supply). Study Continuation Criteria (Section 8.3) will be reviewed prior to the second IP administration in the event of a prolonged Holding Period to confirm the subject is able to receive IP administration at Week 48. The AAV8 TAb assay should be repeated if more than CCI have elapsed since the last measurement (i.e., in the unlikely event that a subject remains in a holding pattern for more than CCI). If proceeding with the second IP administration, the timing of all subsequent visits and assessments (Table 4 and Table 5) should be anchored to the date of the second IP administration.
- **The Follow-up Period (Week 48 through Week 144):** Study assessments during the Follow-up Period will further characterize the efficacy and safety of DTX401 administration to inform the overall risk -benefit profile. The subjects, investigators, site study teams and a dedicated site-facing Sponsor study team will remain blinded until the last subject completes their Week 96 visit or early withdrawal visit.
- **Early Withdrawal (EW):** If a subject plans to leave or will be removed from the study, the subject will be requested to complete Early Withdrawal assessments as specified in Table 3.

Upon completion of this study (Week 144 or Early Withdrawal), all subjects who receive DTX401 will be asked to enroll in a long-term follow-up study (GSDIa Disease Monitoring Program [DMP]) to evaluate the long-term safety and effectiveness of DTX401 for at least 10 years after DTX401 administration.

A study design schematic for Study DTX401-CL301 is presented in Figure 1.

Figure 1: Study Design Schematic, Study DTX401-CL301



CGM, continuous glucose monitoring; D, day; DMP, disease monitoring program; eDiary, electronic diary (for tracking cornstarch, diet intake, and SMBG); IP, investigational product (DTX401 or placebo); RP, randomization period; SCR, screening; SMBG, self-monitoring blood glucose; W, week

Number of Sites: Approximately 23 global study sites in North America, Europe, and Brazil

Number of Subjects: Approximately 50 subjects will be enrolled and randomly assigned in a 1:1 ratio to receive DTX401 (n = 25) or placebo (n = 25). Approximately 20 subjects 8 to < 18 years of age will be enrolled. Randomization will be stratified by age (< 18 years vs ≥ 18 years) and Baseline percentage of values in the target blood glucose range (< 60%, ≥ 60% and ≤ 85%, > 85%).

Population:

Eligible individuals must meet all of the following criteria, unless otherwise noted, during Screening and Randomization:

1. Male and female patients ≥ 8 years of age at the time of informed consent or assent.
2. Subject has a diagnosis of GSDIa confirmed by deficient enzymatic activity (on liver biopsy), or by molecular testing of G6PC gene revealing 2 pathogenic mutations. In the case where only a single pathogenic mutation is identified, clinical diagnosis is compatible with GSDIa and absence of characteristic features of GSDIb (ie, chronic neutropenia, inflammatory bowel disease).
3. Subject is currently receiving a therapeutic regimen of cornstarch (or equivalent), following international guidance/recommendations (Appendix 1) with stable nutrition, glycemic, and clinical status, as evidenced by:
    a. No more than a 10% variation in weekly average daily cornstarch (or equivalent) intake over the last 4 weeks.
    b. No more than a 25% variation in weekly average daily non-cornstarch carbohydrate over the last 4 weeks.
    c. No more than 15% variation in weekly percentage of values in the target blood glucose range (60-120 mg/dL) over the last 4 weeks as measured by CGM and corroborated by SMBG. If adequate corroboration is not observed, this assessment should be made by SMBG.
    d. No hospitalization for hypoglycemia and no severe hypoglycemic event (SHE) during the 4-week period preceding randomization and dosing (see Section 10.4.2 for more detail on SHE), notwithstanding events of hypoglycemia due to unavoidable and unforeseeable events (eg, infection, trauma) that transiently prevent the subject from tolerating enteral intake or acutely change the subject's metabolic demands, provided that the subject quickly returns to their prior physiologic state.
4. Subject is willing and able to comply with study procedures, requirements, and study medication, including periodic inpatient hospitalization or admission in a research facility; CFC studies; frequent blood collection; wearing a CGM device for the duration of the study (and excluding the use of any non-study CGM or flash glucose device); performing capillary glucose measurements according to the protocol using a study -approved glucometer (and excluding the use of any other glucometer); completing an eDiary to track daily cornstarch, diet intake, and reasons for doing SMBG routinely throughout the study as required by the protocol; and completing patient-reported questionnaires. Subject must strictly comply with prednisolone/placebo prednisolone prescription including changes in prescription that may be implemented during the study

by the Investigator, if needed. (See Section 9.2, Prednisolone Taper.) If < 18 years (or as required by region), has a parent or legal guardian willing and able to assist with study requirements.

5. From the period following informed consent through the duration of participation in the study, female subjects of childbearing potential and fertile male subjects must consent to use highly effective contraception as defined by the Food and Drug Administration (FDA) and Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (Version 1.1 dated 21 Sep 2020). Female subjects must agree not to become pregnant and male subjects must agree not to father a child or donate sperm for at least 48 weeks after the last dose of IP if they decide to withdraw early from the study.
6. Subject is willing and able to provide written informed consent after the study has been explained and before any study-related procedures are performed. If < 18 years (or as required by region), willing and able to provide written assent and have a parent or legal guardian willing and able to provide written informed consent after the study has been explained and before any study-related procedures are performed.

Eligible individuals must not meet any of the following criteria, unless otherwise noted, during Screening and Randomization period:

1. Detectable pre-existing antibodies to the AAV8 capsid during Screening.
2. History of liver transplant, including hepatocyte cell therapy/transplant.
3. History of severe hepatic fibrosis or cirrhosis as evidenced by any of the following: portal hypertension, ascites, splenomegaly, esophageal varices, hepatic encephalopathy, or a liver biopsy with evidence of stage III fibrosis.
4. Presence of liver adenoma > 5 cm in size or presence of liver adenoma > 3 cm and ≤ 5 cm in size with a documented annual growth rate of ≥ 0.5 cm per year.
5. Significant hepatic injury or dysfunction as evidenced by imaging or any of the following laboratory abnormalities from 2 consecutive samples (collected at least 4 weeks apart). Liver function tests may be repeated during Screening at the Investigator's discretion; those with initially abnormal values may be retested and the subject will qualify for this criterion if the most recent results during Screening are within the allowed range:
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × the upper limit of normal (ULN)
   - Total bilirubin > ULN unless the subject has Gilbert syndrome
   - Alkaline phosphatase > ULN, with gamma-glutamyl transferase > ULN
6. Presence or history of hepatitis B virus infection, hepatitis C virus infection, or both.

7. Non-fasting triglycerides ≥ 1000 mg/dL. For the purposes of this study, non-fasting refers to the longest fasting period that each individual subject is able to tolerate. Depending on the meal and cornstarch schedule, the blood draw could occur in the morning before breakfast or before the first dose of cornstarch. Triglycerides may be repeated during the Screening Period at the Investigator's discretion and those with abnormal values may be retested. The study subject will qualify for this criterion if the most recent results during Screening are within the allowed range.
8. Human immunodeficiency virus infection AND any of the following: CD4+ cell count < 350 cells/mm3, change in antiretroviral therapy regimen within 6 months before baseline, or plasma viral load > 200 copies/mL on 2 separate occasions as measured by polymerase chain reaction.
9. Presence or history of any disease or condition that, in the Investigator's opinion, would interfere with the subject's safety or ability to participate in the study or would significantly affect interpretation of study results. This includes any intercurrent febrile or nonfebrile illness including common viral infections, epidemic influenza and other viral illnesses, and Coronavirus disease 2019 (COVID-19) until full clinical recovery.
10. Female subjects of childbearing potential who have a positive pregnancy test, who are unwilling to use contraception, or are unwilling to have additional pregnancy tests during the study.
11. Pregnant, breastfeeding, or planning to become pregnant (self or partner) at any time during the study.
12. Presence or history of any hypersensitivity to the excipients of DTX401 or placebo or to prednisolone, or inability to swallow capsules, that in the judgment of the Investigator places the subject at increased risk for adverse effects.
13. Current or previous participation in another gene transfer study.
14. Use of any IP or investigational medical device within 3 months preceding screening or planning to use at any time during the study.
15. History of illicit drug use within 60 days prior to Screening or positive results from a 9-panel urine drug screen prior to dosing and completed at 2 time points at least 4 weeks apart. Positive results that are due to a prescribed medication may be allowed if not impacting glycemic control and liver function and after agreement with the Sponsor. For the purposes of this protocol, use of recreational cannabis products is not allowed, even if legal in the region where the patient lives.

Study Continuation Criteria

All subjects will be evaluated according to Study Continuation Criteria prior to their second IP administration at Week 48. Subjects who meet any of the following exclusion criteria may not receive blinded IP at Week 48 but will complete all other Week 48 assessments. The decision to continue with study assessments beyond Week 48 will be determined by the Investigator and Sponsor Medical Monitor, based on the following:

1. Positive antibodies to AAV8 capsid, collected at Week 36 (or during the Holding Period if required) if the subject was allocated to placebo at Baseline.

2. Liver tests that meet DILI thresholds for serious liver injury (Table 11), or any clinically significant changes from baseline in liver tests that in the judgment of the PI or unblinded Medical Monitor would interfere with safety of blinded IP infusion at Week 48 or would significantly affect interpretation of safety and efficacy results.
3. Presence of any abnormality, in the Investigator's opinion, that would interfere with the subject's safety or ability to continue participating in the study or would significantly affect interpretation of study results.
4. Female subjects of childbearing potential and fertile male subjects unwilling to continue to use highly effective contraception as defined by the Food and Drug Administration (FDA) and Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (Version 1.1 dated 21 Sep 2020).
5. Female subjects unwilling to continue pregnancy testing or who plan to become pregnant or breastfeed within 48 weeks after the last dose of IP.
6. Male subjects unwilling to agree not to father a child or donate sperm for at least 48 weeks after the last dose of IP.

Due to the nutrition adjustments throughout the treatment period, nutrition, glycemic and expected metabolic stability do not form part of the Study Continuation Criteria. However, the Investigator should discuss any concerns about nutritional, glycemic or metabolic stability (eg, severe hypoglycemia, significantly elevated triglycerides, etc.) with the unblinded Medical Monitor before proceeding with the second IP administration at Week 48.

Study Interventions:

Table 2: Study Interventions

Intervention	DTX401	Placebo for DTX401 (Normal Saline)	Prednisolone	Placebo for Prednisolone	Acetaminophen/ Paracetamol	2nd generation H1 antagonist (cetirizine or equivalent)	H2 antagonist (famotidine or equivalent)
Dose formulation	2.8×10^{13} GC/mL[a]	0.9 % sodium chloride	5 mg or 10 mg gelatin capsules	Tablets matching prednisolone	Tablet	Tablet	Tablet
Unit dose strength/ dosage level	1×10^{13} GC/kg, single infusion	n/a	Weight-based dose taper (Section 9.2)	n/a	12.5 mg/kg, up to a max dose of 1 g	10 mg for cetirizine	0.5 mg/kg, up to max dose of 40 mg for famotidine
Route of administration	IV infusion	IV infusion	Oral	Oral	Oral	Oral	Oral
Use	Experimental agent	Placebo comparator to DTX401	Prophylaxis: prevention of vector-induced hepatic effects	Placebo to maintain study blind	Premedication[b]	Premedication[b]	Premedication[b]

[a] Target concentration measured using a ddPCR method; release acceptance criteria: $\geq 7.3 \times 10^{12}$ to $\leq 9.0 \times 10^{13}$ GC/mL
[b] The study site will supply premedication that will be obtained locally.
ddPCR, Droplet Digital polymerase chain reaction; GC, genome copies; IV, intravenous; n/a, not applicable

Duration of Subject Participation:

The planned study duration is approximately 162 weeks (with possible extension if a subject enters a holding period), including the following:

- Pre-dosing Period of up to 18 weeks: Subjects may be randomized as soon as nutrition optimization and 4 consecutive weeks of diet, cornstarch, and blood glucose control stability are demonstrated. Subjects will have up to 16 weeks to achieve nutritional optimization and stability prior to randomization and approximately 10 days from randomization to dosing. See details in Section 7.1.1.
- PEAP: 48 weeks
- Follow-up Period of 96 weeks

Upon completion of this study (EOS or Early Withdrawal), all subjects who receive DTX401 will be asked to enroll in a long-term follow-up study (GSDIa DMP) to evaluate the long-term safety and effectiveness of DTX401 for at least 10 years after DTX401 administration.

Table 3: Schedule of Events, Year 1

Period	**Screen**	**Rand**	**BL**	**Primary Efficacy Analysis Period**														
Visit Time (Day/Week)	**D -122 to D -10**	**D -10**	**D0**	**D1 to D2 (Dosing Visit)**		**D15 (Start Steroids)**	**W4**	**W5**	**W6**	**Weekly: W7 to W11**	**D84/ W12**	**D168/ W24**	**D210/ W30**	**D252/ W36**	**D294/ W42**	**D336/ W48**	**Holding Visit(s)[a]**	**EW**
Visit Window (Days)	**-**	**-**	**-**	**Pre dose**	**Dose/ Post dose**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±14**	**±14**	**±14**	**±14**	**+7**	**±14**	**-**
Visit Type	**oPt**	**Phone**	**InPt**	**InPt**	**InPt[b]**	**Phone**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/HH[c]**	**oPt/ HH[c]**	**Phone**	**InPt**	**Phone**	**InPt**	**oPt/ HH[c]**	**InPt**
Assessments																		
Informed consent	X																	
Review eligibility criteria	X	X	X															
Demographics	X																	
Relevant medical history	X																	
GSDIa medical history	X																	
Height[d]	X		X								X	X		X		X		X
Weight	X		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	X	X	X	X	X	X	X
Dispense/ administer oral prednisolone/ placebo kit[e]					X	X												
Collect oral prednisolone/ placebo kit											X							
Prednisolone/placebo monitoring phone calls						X (Refer to Table 14 for specific timing of phone calls)													

Period	Screen	Rand	BL	Primary Efficacy Analysis Period													
Visit Time (Day/Week)	D -122 to D -10	D -10	D0	D1 to D2 (Dosing Visit)		D15 (Start Steroids)	W4	W5	W6	Weekly: W7 to W11	D84/ W12	D168/ W24	D210/ W30	D252/ W36	D294/ W42	D336/ W48	Holding Visit(s)[a]	EW
Visit Window (Days)	-	-	-	Pre dose	Dose/ Post dose	-	±3	±3	±3	±3	±3	±14	±14	±14	±14	+7	±14	-
Visit Type	oPt	Phone	InPt	InPt	InPt[b]	Phone	oPt/ HH[c]	oPt/ HH[c]	oPt/ HH[c]	oPt/ HH[c]	oPt/HH[c]	oPt/ HH[c]	Phone	InPt	Phone	InPt	oPt/ HH[c]	InPt
Early morning cortisol and ACTH						To be obtained 24 hours after completing the prednisolone/placebo taper; any abnormal levels should be reviewed by the CIC												
GSD FAD eDiary[f]	X		X													X		X
GSD FAD (weekly version)[f]																X		
PGIS[f]	X		X									X		X		X		X
PGIC[f]	X											X		X		X		X
PGIC-CTT[f]																X		X
EQ-5D-5L/ EQ-5D-Y[g]			X											X		X		X
HEOR assessments			X											X		X		X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements[h]	X		X	X	X[h]		X	X	X	X	X	X		X		X	X	X
Complete physical examination[i]	X															X		X
Targeted physical examination[i]			X								X	X		X				
12-lead ECG	X															X		X
G6PC genotyping[j]	X																	
HBV, HCV, HIV	X																	

Period	**Screen**	**Rand**	**BL**	**Primary Efficacy Analysis Period**														
Visit Time (Day/Week)	**D -122 to D -10**	**D -10**	**D0**	**D1 to D2 (Dosing Visit)**		**D15 (Start Steroids)**	**W4**	**W5**	**W6**	**Weekly: W7 to W11**	**D84/ W12**	**D168/ W24**	**D210/ W30**	**D252/ W36**	**D294/ W42**	**D336/ W48**	**Holding Visit(s)[a]**	**EW**
Visit Window (Days)	**-**	**-**	**-**	**Pre dose**	**Dose/ Post dose**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±14**	**±14**	**±14**	**±14**	**+7**	**±14**	**-**
Visit Type	**oPt**	**Phone**	**InPt**	**InPt**	**InPt[b]**	**Phone**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/HH[c]**	**oPt/ HH[c]**	**Phone**	**InPt**	**Phone**	**InPt**	**oPt/ HH[c]**	**InPt**
Serum pregnancy test (only for women of childbearing potential)	X																	
Urine pregnancy test (for women of childbearing potential)[k]			X				X			X (W8)	X	X		X		X	X	X
Standard clinical chemistry panel-Central Lab[l]	X		X				X	X	X	X	X	X		X		X	X	X
Lactate [m]							X		X		X							
Standard clinical chemistry panel-Local Lab[l]			X[n]	X	X[o]									X[n]		X[n]		
STAT glucose and lactate during CFC[p]			X											X		X		
Cortisol and other HPA axis tests as needed[q]														X (W35)		X (W47)		
Cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine, and ketones during CFC[p]			X											X		X		

Period	**Screen**	**Rand**	**BL**	**Primary Efficacy Analysis Period**													
Visit Time (Day/Week)	**D -122 to D -10**	**D -10**	**D0**	**D1 to D2 (Dosing Visit)**		**D15 (Start Steroids)**	**W4**	**W5**	**W6**	**Weekly: W7 to W11**	**D84/ W12**	**D168/ W24**	**D210/ W30**	**D252/ W36**	**D294/ W42**	**D336/ W48**	**Holding Visit(s)[a]**	**EW**
Visit Window (Days)	**-**	**-**	**-**	**Pre dose**	**Dose/ Post dose**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±14**	**±14**	**±14**	**±14**	**+7**	**±14**	**-**
Visit Type	**oPt**	**Phone**	**InPt**	**InPt**	**InPt[b]**	**Phone**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/ HH[c]**	**oPt/HH[c]**	**oPt/ HH[c]**	**Phone**	**InPt**	**Phone**	**InPt**	**oPt/ HH[c]**	**InPt**
Hematology, coagulation panel, urinalysis- Local Lab			X													X		
Hematology, coagulation panel, urinalysis- Central Lab	X		X				X[r]		X[r]		X	X		X		X		X
9-panel urine drug screen[s]	X																	
24-hour urine collection[t]			X													X		X
AAV8 TAb assay[u]	X													X				
AAV8 binding antibody IgG testing (ELISA)			X				X[v]		X[v]		X	X[v]				X		X
Cell-mediated immune response to G6Pase (ELISpot)			X						X[v]		X							X
Complement Activity (C3, C4, SC5b-9, CH50, AH50, MBL)			X		X[w]											X		
Serum tryptase			X		X[w]											X		
Anti-G6Pase antibody assay			X								X					X		X
Optional future research sample[x]			X								X	X				X		X
Liver ultrasound[y]	X													X				

Period	Screen	Rand	BL	Primary Efficacy Analysis Period														
Visit Time (Day/Week)	D -122 to D -10	D -10	D0	D1 to D2 (Dosing Visit)		D15 (Start Steroids)	W4	W5	W6	Weekly: W7 to W11	D84/ W12	D168/ W24	D210/ W30	D252/ W36	D294/ W42	D336/ W48	Holding Visit(s)[a]	EW
Visit Window (Days)	-	-	-	Pre dose	Dose/ Post dose	-	±3	±3	±3	±3	±3	±14	±14	±14	±14	+7	±14	-
Visit Type	oPt	Phone	InPt	InPt	InPt[b]	Phone	oPt/ HH[c]	oPt/ HH[c]	oPt/ HH[c]	oPt/ HH[c]	oPt/HH[c]	oPt/ HH[c]	Phone	InPt	Phone	InPt	oPt/ HH[c]	InPt
SMBG[z]	X	X	X									X	X	X	X	X		X
CGM[aa]	X	X	X									X	X	X	X	X		X
Assessment of prescribed cornstarch and cornstarch intake[bb]	X	X	X									X	X	X	X	X		X
Assessment of prescribed diet and dietary intake[bb]	X	X	X									X	X	X	X	X		X
Controlled fasting challenge[cc]			X											X		X		X
CFC Questionnaire[cc]			X											X		X		X
Subject entry/exit interview			X													X		X
Subject number assigned in IRT[dd]	X																	
Randomization in IRT		X																
IP administration scheduling in IRT[ee]		X													X[ff]			
Premedication[gg]				X														
IP infusion					X													

[a] The holding period consists of clinical or home health visits every 12 weeks as needed to allow for continued subject follow-up after Week 48 assessments and prior to the second dosing visit (e.g., due to interruption to IP supply).

[b] The duration of inpatient observation including the assessment of vital signs begins with the start of IP administration, and is a minimum of 6 hours after dosing is complete. Subjects may be discharged when all post-IP infusion protocol assessments are complete and the Investigator determines that the subject is clinically stable and safe to be discharged. Details can be found in Section 9.1.4.

[c] Phone calls should be conducted by the site study team. Phone calls on days of Home Health visits should be conducted with Home Health visits to ensure AE collection, concomitant medication review, and assessment of diet and cornstarch.
[d] In subjects ≥ 18 years of age, height will be assessed only at Screening, Baseline, Week 48 and Early Withdrawal visits.
[e] Subjects randomly assigned to DTX401 in Year 1 will receive an oral prophylactic prednisolone regimen; subjects randomly assigned to placebo IP infusion will receive a matching oral placebo regimen to maintain the study blind. Oral prophylactic prednisolone or matching placebo will be initiated 14 days after IP administration (Day 15).
[f] The GSD FAD eDiary will be completed electronically by the subject every morning and evening for 14 days before the Baseline Visit and for 7 days before each applicable postbaseline study visit. The GSD FAD (weekly version) will be completed on paper at the clinic site visit for each applicable post-baseline study visit. The PGICand PGIS will be completed electronically via the eDiary on the day before the applicable study visit. During the Screening Period, the PGIS will be performed twice and the PGIC will be performed once; these assessments will be performed once at all other applicable study visits. If PGIC and/or PGIS data have not been reported in the eDiary preceding the applicable study visit, the clinic site staff will have the subject complete the PGIC and/or PGIS on paper at the time of the study visit. The PGIC-CTT will be completed on paper at the applicable postbaseline study visits.
[g] The EQ-5D-5L (or EQ-5D-Y for subjects < 18 years of age) will be completed on paper at the study visit before any invasive study assessments or procedures.
[h] Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in °C. Vital sign measurements will be performed at every visit before any additional assessments are completed except on days of IP infusion when they will be performed more frequently as detailed in Section 9.1.4.
[i] Complete physical examination will include assessment of the head, eyes, ears, nose, and throat; skin; abdomen with documentation of liver and spleen size; and endocrine, metabolic, peripheral and central nervous systems, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems. Targeted physical examination will include assessment of the skin; abdomen with documentation of liver and spleen size; and respiratory, cardiovascular, and gastrointestinal systems. Tanner pubertal stage development will be assessed at Baseline and in all postdosing inpatient visits for pediatric subjects < 18 years of age. Safety assessments will include evaluation for sensory neuropathy symptoms; if such symptoms are identified, they will be recorded as adverse events and followed by a thorough neurological examination and additional nerve conduction and imaging studies as needed.
[j] *G6PC* mutation analysis will not be waived unless results have been obtained previously from the same laboratory conducting the analysis and are in the subject's medical records.
[k] A serum pregnancy test must also be conducted in the event of a positive urine pregnancy test result.
[l] Standard clinical chemistry assessments required at each study visit are listed in Table 19. Liver function tests and triglyceride levels may be repeated during the Screening Period at the Investigator's discretion to confirm eligibility. Samples for clinical chemistry should be collected after vital signs and other noninterventional assessments have been performed and at least 2 to 4 hours after the subject's last meal. If liver function tests between Weeks 4 and 11 are stable, the assessment schedule between those visits may be reduced from weekly to every two weeks at the Investigator's discretion.
[m] To be collected locally. When local collection is not feasible, may be collected by home health care vendor.
[n] On days when CFC is performed, clinical chemistry samples will be sent to both the central and local laboratories. Results from the local laboratory must be reviewed before starting the CFC or before IP administration.
[o] On the day of IP administration, a standard clinical chemistry panel will be collected approximately 0.5 and 2 hours after the start of the IP infusion (Local Laboratory).
[p] Samples specific to the CFC will be collected at the beginning and end of the CFC or more frequently at the Investigator's discretion. During the CFC, subjects should be wearing their CGM and capillary glucose should be assessed and recorded at each CFC time point. During CFC, to maintain subject safety, an additional CGM device offering real-time readings may be worn by the subject at the Investigator's discretion. For pediatric subjects weighing < 45 kg, samples other than glucose and lactate are optional and per Investigator's discretion based on subject's general status and recent blood counts. When collection is possible and in line with pediatric blood volume limits, assessments that can be performed using the same collection tube and least amount of blood volume should be prioritized. Details are provided in Section 10.2.4.
[q] Morning cortisol and other exploratory tests of the HPA axis should be performed as necessary prior to the CFC. A blood sample for measurement of morning cortisol levels or other HPA axis tests will be collected approximately 1 week before the Week 36 and Week 48 Visit. If the test cannot be performed remotely, it can be done on the first day of admission if the results will be available prior to the start of the CFC. Morning cortisol levels and HPA axis tests may be performed as needed at additional visits as indicated and in most cases will be conducted 1 week prior to the visit.
[r] Urinalysis will not be performed at the Week 4 or 6 visits.
[s] During the Screening Period, a 9-panel urine drug screen will be completed at 2 time points at least 4 weeks apart.
[t] Urine will be collected for 24 hours prior to the CFC at Baseline and Week 48 and sent to the Central Laboratory for analysis. A sample from the urine collection performed at Baseline and prior to each CFC will be used for Hex4 assessment. Additional samples may be conserved for future biomarker research.
[u] It is recommended that the Screening sample be collected at the time when written informed consent is provided; the presence of detectable pre-existing antibodies to the AAV8 capsid would exclude a subject from study participation, and the subject would not be eligible for re-screening. Positive AAV8 TAb assay samples will be further analyzed with the AAV assay (immunogenicity assay) for future DTX401-related

research. The AAV8 TAb assay should be repeated prior to the second IP administration if more than 6 months have elapsed since the last measurement (i.e., in the unlikely event that a subject remains in a holding pattern for more than 6 months).

[v] For pediatric subjects weighing < 45 kg, assessments at these weeks are optional per the Investigator's discretion based on subject's general status and recent blood counts. Efforts should be made to collect as frequently as is possible without exceeding pediatric blood volume limits.

[w] To be measured post-dose only in subjects who experience an infusion-related reaction 30 to 120 minutes after the start of the reaction, and once again at least 24 hours after the symptoms have resolved. The timing of sample collection should be documented. If there are challenges to obtaining blood samples, the order of sampling priority is 1) tryptase, C3, C4, CH50, 2) AH50 and MBL, 3) SC5b-9.

[x] Optional blood collection may be performed for subjects who consent to sample collection for exploratory future research if this sample would not exceed maximum blood sampling volume.

[y] At investigator's discretion, an alternative imaging modality, e.g. CT or MRI, can be used in place of liver ultrasound if more clinically appropriate.

[z] SMBG must be performed at least 4 times a day during screening and in the 1-week period prior to each postbaseline scheduled visit at Weeks 24, 30, 36, 42 and 48. Additional SMBG assessments may be performed as per standard of care or at the discretion of the Investigator or if the subject is symptomatic. Subjects are only required to record the reason for performing SMBG in the eDiary if they are symptomatic. SMBG measurements taken for routine standard of care where they are not symptomatic do not need to be recorded in the eDiary.

[aa] It is recommended that subjects wear the CGM device and connect to the study issued computer to transfer CGM transmitter data collection throughout the study. CGM device must be worn for at least 4 weeks leading up to Weeks 24, 30, 36, 42 and 48 visits.

[bb] Subjects must record their cornstarch and diet intake daily for at least 4 weeks before the Baseline Visit. During the study and before scheduled visits, particularly prior to the Week 24, 30, 36 and 42 visits, subjects will record their cornstarch intake daily for at least 1 week before each of these study visits. Subjects will record their cornstarch intake daily for at least 4 weeks before the Week 48 visit. Subjects must record their daily diet for a full 3 days prior to the Week 24, 30, 36, 42, and 48 visits. All cornstarch and diet prescriptions will be recorded in EDC at Screening, Baseline, and at scheduled visits. Section 10.2.1 provides further details. The Investigator should review the SMBG and CGM data and other data collected from the eDiary, EDC, and confirmatory exchanges with the subject at least once a week to manage the subject's prescribed cornstarch and diet regimen. Study endpoint analyses will use the SMBG, CGM, and cornstarch intake data from 1 week before each study visit, so preferably the prescribed regimen should not be changed within 2 weeks before a planned study visit. If a change to the cornstarch or diet regimen is necessary during that time, contact the Medical Monitor to discuss whether the planned study visit should be delayed. Section 7.1.2, Section 10.2.2 and Section 10.2.3 provide further details on cornstarch regimen modifications and SMBG and CGM procedures, respectively.

[cc] The CFC requires a 24-hour inpatient hospitalization or admission in a research facility and includes a dinner meal personalized for each subject, followed by a prefasting cornstarch dose and up to 15 hours of fasting. Blood samples will be collected. Further details about CFC-specific procedures and timing of collection of the CFC questionnaires are provided in Section 10.2.4.

[dd] The site should enter the subject into the IRT system after the ICF has been signed.

[ee] The site will schedule the IP infusion date in the IRT at least 10 business days before the IP infusion to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site.

[ff] The unblinded site pharmacist and the unblinded Clinical Trial Manager will review results from the Week 36 for eligibility for Week 48 IP administration. The Investigator will review the Week 36 assessments as soon as they are available to confirm that the subject is eligible to receive IP administration at Week 48. If there is evidence of any change from Baseline in disease status or overall well-being that would preclude safe administration of DTX401, the Investigator will consult the blinded Medical Monitor.

[gg] Premedication to be administered 30 to 60 minutes prior to the start of blinded IP infusion.

Note: Microsampling for blood collections will be prioritized in subjects ≤ 12 years of age

AAV8, adeno-associated virus serotype 8; ACTH, adrenocorticotropic hormone; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; CIC, Central Independent Committee; CFC, controlled fasting challenge; CGM, continuous glucose monitoring; D, day; ECG, electrocardiogram; EDC, electronic data capture; eDiary, electronic diary; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immune absorbent spot; EQ-5D-(5L/Y), EuroQol- 5 Dimension (5-level/youth version); EW, early withdrawal; G6Pase, glucose-6-phosphatase (protein); *G6PC*, glucose-6-phosphatase (gene); GSD FAD, Glycogen Storage Disease Functional Assessment Diary; GSDIa, glycogen storage disease type Ia; HBV, hepatitis B virus; HCV, hepatitis C virus; HEOR, health economics outcomes research; HH, home healthcare visit; HIV, human immunodeficiency virus; HPA, hypothalamic-pituitary-adrenal; ICF, informed consent form; IgG, immunoglobulin G; IGFBP1, insulin like growth factor binding protein 1; InPt, inpatient visit; IP, investigational product (DTX401 or placebo); IRT, interactive response technology; oPt, outpatient visit; PGIC, Patient Global Impression of Change; PGIC, Patient Global Impression of Change – Cornstarch Treatment Tolerance; PGIS, Patient Global Impression of Severity; RAND, Randomization Visit; SAE, serious adverse event; SCRN, Screening Period; SMBG, self-monitored blood glucose; STAT, as quickly as possible; TAb, total antibody; W, week

Table 4: Schedule of Events, Year 2

Period	**W48 Dosing Visit[a]**		**Start Steroids**											
Visit Time (Day/Week)[b]	**D337-D338 (+7)**		**D352**	**W52**	**W53**	**W54**	**Weekly: W55 to W59**	**W60**	**W72**	**W78**	**W84**	**W90**	**W96**	**EW**
Visit Window (Days)	**Predose**	**Dosing/ Postdose**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±14**	**±14**	**±14**	**±14**	**+7**	**-**
Visit Type	**InPt**	**InPt[c]**	**Phone**	**oPt/HH[d]**	**oPt/ HH[d]**	**oPt/HH[d]**	**oPt/ HH[d]**	**oPt/HH[d]**	**oPt/HH[d]**	**Phone**	**InPt**	**Phone**	**InPt**	**InPt**
Height[e]								X	X		X		X	X
Weight	X							X	X		X		X	X
Relevant concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X
Review eligibility criteria	X[f]													
Dispense/administer oral prednisolone/ placebo kit[g]		X	X											
Collect oral prednisolone/placebo kit								X						
Prednisolone/placebo monitoring phone call			X (Refer to Table 14 for specific timing of phone calls)											
Early morning cortisol and ACTH			To be obtained 24 hours after completing the prednisolone/placebo taper; any abnormal levels should be reviewed by the CIC											
GSD FAD eDiary[h]													X	X
GSD FAD (weekly version)[h]													X	
PGIS[h]									X		X		X	X
PGIC[h]									X		X		X	X
PGIC-CTT[h]													X	X
EQ-5D-5L/ EQ-5D-Y[i]											X		X	X
HEOR assessments											X		X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	W48 Dosing Visit[a]		Start Steroids											
Visit Time (Day/Week)[b]	D337-D338 (+7)		D352	W52	W53	W54	Weekly: W55 to W59	W60	W72	W78	W84	W90	W96	EW
Visit Window (Days)	Predose	Dosing/ Postdose	-	±3	±3	±3	±3	±3	±14	±14	±14	±14	+7	-
Visit Type	InPt	InPt[c]	Phone	oPt/HH[d]	oPt/ HH[d]	oPt/HH[d]	oPt/ HH[d]	oPt/HH[d]	oPt/HH[d]	Phone	InPt	Phone	InPt	InPt
Vital sign measurements[j]	X	X		X	X	X	X	X	X		X		X	X
Complete physical examination[k]													X	X
Targeted physical examination[k]								X	X		X			
12-Lead ECG													X	X
Urine pregnancy test (women of childbearing potential only)				X			X (W56 only)	X	X		X		X	X
Standard clinical chemistry panel- Central Lab[l]				X	X	X	X	X	X		X		X	X
Lactate[m]				X		X		X						
Standard clinical chemistry panel - Local Lab[m]	X	X[n]									X[o]		X[o]	X[o]
STAT glucose and lactate during CFC[p]											X		X	X
Cortisol and other HPA axis tests as needed[q]											X (W83)		X (W95)	
Cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine, and ketones during CFC[q]											X		X	X
Hematology, coagulation panel, urinalysis - Central Lab				X[r]		X[r]		X	X		X		X	X
24-hour urine collection[s]													X	X
AAV8 binding antibody IgG testing (ELISA)				X[t]		X[t]		X	X[t]				X	X

Period	W48 Dosing Visit[a]		Start Steroids											
Visit Time (Day/Week)[b]	D337-D338 (+7)		D352	W52	W53	W54	Weekly: W55 to W59	W60	W72	W78	W84	W90	W96	EW
Visit Window (Days)	Predose	Dosing/ Postdose	-	±3	±3	±3	±3	±3	±14	±14	±14	±14	+7	-
Visit Type	InPt	InPt[c]	Phone	oPt/HH[d]	oPt/ HH[d]	oPt/HH[d]	oPt/ HH[d]	oPt/HH[d]	oPt/HH[d]	Phone	InPt	Phone	InPt	InPt
Cell-mediated immune response to G6Pase (ELISpot)						X[t]		X						X
Anti-G6Pase antibody assay								X					X	X
Complement Activity (C3, C4, SC5b-9, CH50, AH50, MBL)[u]		X												
Serum Tryptase[u]		X												
Optional future research sample[v]								X	X				X	X
Liver Ultrasound[w]													X	X
SMBG[x]									X	X	X	X	X	X
CGM[y]									X	X	X	X	X	X
Assessment of prescribed cornstarch and cornstarch intake[z]									X	X	X	X	X	X
Assessment of prescribed diet and dietary intake[z]									X	X	X	X	X	X
Controlled fasting challenge[aa]											X		X	X
CFC Questionnaire[aa]											X		X	X
Subject exit interviews													X	X
Premedication[bb]	X													
IP infusion		X[n]												

[a] The Week 48 Visit cannot occur earlier than 48 weeks after the Day 1 IP administration.
[b] The timing of all Year 2 visits and assessments should be anchored to the date of the Week 48 dosing visit. For eg, the Week 60 visit is due to occur 12 weeks following administration of second blinded IP infusion in Year 2.

[c] The duration of inpatient observation after IP administration including assessment of vital signs begins with the start of IP administration, and is a minimum of 6 hours after dosing is complete. Subjects may be discharged when all post-IP infusion protocol assessments are complete and the Investigator determines that the subject is clinically stable and safe to be discharged. Details can be found in Section 9.1.4.

[d] Phone calls should be conducted by the site study team. Phone calls on days of Home Health visits should be conducted with Home Health visits to ensure AE collection, concomitant medication review, and assessment of diet and cornstarch.

[e] In subjects ≥ 18 years of age, height will be assessed only at Week 96 and Early Withdrawal visits

[f] The Investigator should confirm that the subject is able to receive IP administration at Week 48. The Investigator will review the Week 36 assessments as soon as they are available to confirm that the subject is eligible to receive IP administration at Week 48. If there is evidence of any change from Baseline in disease status or overall well-being that would preclude safe administration of DTX401, the Investigator will consult the Medical Monitor.

[g] Subjects receiving DTX401 at Week 48 will receive an oral prophylactic prednisolone regimen; subjects receiving placebo IP infusion at Week 48 will receive a matching oral placebo regimen in order to maintain the study blind. Subjects will be instructed to administer the first dose of prophylactic corticosteroids 14 days after IP administration (Day 352).

[h] The GSD FAD will be completed electronically every morning and evening for 7 days before each applicable study visit. The GSD FAD (weekly version) will be completed on paper at the clinic site visit for each applicable post-baseline study visit. The PGIC and PGIS will be completed electronically via the eDiary on the day before the applicable study visit. If PGIC and/or PGIS data have not been reported in the eDiary preceding the applicable study visit, the clinic site staff will have the subject complete the PGIC and/or PGIS on paper at the time of the study visit. The PGIC-CTT will be completed on paper at the applicable postbaseline study visits.

[i] The EQ-5D-5L (or EQ-5D-Y for subjects < 18 years of age) will be completed on paper at the study visit before any invasive study assessments or procedures.

[j] Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in °C. Vital sign measurements will be performed before any additional assessments are completed, except on the day of IP infusion when they will be performed more frequently, as detailed in Section 9.1.4.

[k] Complete physical examination will include assessment of the head, eyes, ears, nose, and throat; skin; abdomen with documentation of liver and spleen size; and endocrine, metabolic, peripheral and central nervous systems, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems. Targeted physical examination will include assessment of the skin; abdomen with documentation of liver and spleen size; and respiratory, cardiovascular, and gastrointestinal systems. Tanner pubertal stage development will be assessed at all postdosing inpatient visits for pediatric subjects < 18 years of age. Safety assessments will include evaluation for sensory neuropathy symptoms; if such symptoms are identified, they will be recorded as adverse events and followed by a thorough neurological examination and additional nerve conduction and imaging studies as needed.

[l] Standard clinical chemistry assessments required at each study visit are listed in Table 19. Samples for clinical chemistry should be collected after vital signs and other noninterventional assessments have been performed and at least 2 to 4 hours after the subject's last meal. If liver function tests between Weeks 52 and 59 are stable, the assessment schedule between those visits may be reduced from weekly to every two weeks at the Investigator's discretion.

[m] To be collected locally. When local collection is not feasible, may be collected by home health care vendor.

[n] On the day of IP administration, a standard clinical chemistry panel will be collected approximately 0.5 and 2 hours after the start of the IP infusion (Local Laboratory).

[o] On days when the CFC will be performed, clinical chemistry samples will be sent to both the central and local laboratories. Results from the local laboratory must be reviewed before starting the CFC or before IP administration.

[p] Samples specific to the CFC will be collected at the beginning and end of the CFC or more frequently at the Investigator's discretion. During the CFC, subjects should be wearing their CGM and capillary glucose should be assessed and recorded at each CFC time point. During CFC, to maintain subject safety, an additional CGM device offering real-time readings may be worn by the subject at the Investigator's discretion. For pediatric subjects weighing < 45 kg, samples other than glucose and lactate are optional and per Investigator's discretion based on subject's general status and recent blood counts. When collection is possible and in line with pediatric blood volume limits, assessments that can be performed using the same collection tube and least amount of blood volume should be prioritized. Details are provided in Section 10.2.4.

[q] Morning cortisol and other exploratory tests of the HPA axis should be performed as necessary prior to the CFC. A blood sample for measurement of morning cortisol levels or other HPA axis tests will be collected approximately 1 week before the Week 84 and Week 96 Visit. If the test cannot be performed remotely, it can be done on the first day of admission if the results will be available prior to the start of the CFC. Morning cortisol levels and HPA axis tests may be performed as needed at additional visits, as indicated, and in most cases will be conducted 1 week prior to the visit.

[r] Urinalysis will not be performed at the Week 52 or 54 visits.

[s] Urine will be collected for 24 hours prior to each CFC and sent to the Central Laboratory for analysis. A sample from the urine collection performed prior to each CFC will be used for Hex4 assessment. Additional samples may be conserved for future biomarker research.

[t] For pediatric subjects weighing < 45 kg, assessments at these weeks are optional per the Investigator's discretion based on subject's general status and recent blood counts. Efforts should be made to collect as frequently as is possible without exceeding pediatric blood volume limits.

[u] To be measured post-dose only in subjects who experience an infusion-related reaction 30 to 120 minutes after the start of the reaction, and once again at least 24 hours after the symptoms have resolved. The timing of sample collection should be documented. If there are challenges to obtaining blood samples, the order of sampling priority is 1) tryptase, C3, C4, CH50, 2) AH50 and MBL, 3) SC5b-9.

[v] Optional blood collection may be performed for subjects who consent to sample collection for exploratory future research if this sample would not exceed maximum blood sampling volume.

[w] At Investigator's discretion, an alternative imaging modality, e.g. CT or MRI, can be used in place of liver ultrasound if more clinically appropriate.

[x] SMBG must be performed at least 4 times a day in the 1-week period prior to visits at Week 72, 78, 84, 90 and 96. Additional SMBG assessments may be performed at the discretion of the Investigator or if the subject is symptomatic. Subjects are only required to record the reason for performing SMBG in the eDiary if they are symptomatic. SMBG measurements taken for routine standard of care where they are not symptomatic do not need to be recorded in the eDiary.

[y] It is recommended that subjects wear the CGM device and connect to the study issued computer to transfer CGM transmitter data collection throughout the study. CGM device must be worn for at least 4 weeks prior to visits at Week 72, 78, 84, 90 and 96.

[z] Subjects must record their cornstarch and diet intake in the eDiary before all scheduled visits. Subjects must record their cornstarch intake daily for at least 1 week prior to visits at Weeks 72, 78, 84 and 90, and at least 4 weeks prior to the Week 96 visit. Subjects must record their daily diet for a full 3 days prior to visits at Weeks 72, 78, 84, 90 and 96. All cornstarch and diet prescriptions will be recorded in EDC at Screening, Baseline, and all visits. Section 10.2.1 provides further details. The Investigator should review the CGM data and other data collected from the eDiary, EDC, and confirmatory exchanges with the subject at least once a week to manage the subject's prescribed cornstarch and diet regimen. Study endpoint analyses will use the SMBG, CGM, and cornstarch intake data from 1 week before each study visit, so preferably the prescribed regimen should not be changed within 2 weeks before a planned study visit. If a change to the cornstarch or diet regimen is necessary during that time, contact the Medical Monitor to discuss whether the planned study visit should be delayed. Section 7.1.2, Section 10.2.2 and Section 10.2.3 provide further details regarding cornstarch regimen modifications and SMBG and CGM procedures, respectively.

[aa] The CFC requires a 24-hour inpatient hospitalization or admission in a research facility and includes a dinner meal personalized for each subject, followed by a prefasting cornstarch dose and up to 15 hours of fasting. Blood samples will be collected. At each CFC, subjects will be asked questions from the CFC questionnaire by site staff relating to symptoms of hypoglycemia. Further details about CFC-specific procedures and timing of collection of the CFC questionnaires are provided in Section 10.2.4.

[bb] Premedication to be administered 30 to 60 minutes prior to the start of blinded IP infusion.

AAV8, adeno-associated virus serotype 8; ACTH, adrenocorticotropic hormone; AE, adverse event; CIC, Central Independent Committee; CFC, controlled fasting challenge; CGM, continuous glucose monitoring; CRF, case report form; D, day; ECG, electrocardiogram; eDiary, electronic diary; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immune absorbent spot; EOS, end of study; EQ-5D-(5L/Y), EuroQol- 5 Dimension (5-level/youth version); EW, early withdrawal; G6Pase, glucose-6-phosphatase (protein); GSD FAD, Glycogen Storage Disease Functional Assessment Diary; HEOR, health economics outcomes research; HH, home healthcare visit; IGFBP1, insulin like growth factor binding protein 1; InPt, inpatient visit; HPA, hypothalamic-pituitary-adrenal; IP, investigational product (DTX401 or placebo); oPt, outpatient visit; PGIC, Patient Global Impression of Change; PGIC, Patient Global Impression of Change – Cornstarch Treatment Tolerance; PGIS, Patient Global Impression of Severity; SAE, serious adverse event; SMBG, self-monitored blood glucose; STAT, as quickly as possible; W, week

Table 5: Schedule of Events, Year 3

Visit Time (Day/Week)	**W108**	**W120**	**W132**	**W144/ EOS**	**EW**
Visit Window (Days)	**±14**	**±14**	**±14**	**±14**	**-**
Visit Type	**oPt/HH[a]**	**oPt/ HH[a]**	**oPt/HH[a]**	**oPt**	**InPt**
Height[b]	X	X	X	X	X
Weight	X	X	X	X	X
Relevant concomitant medications	X	X	X	X	X
GSD FAD eDiary[c]				X	X
PGIS[c]		X		X	X
PGIC[c]		X		X	X
PGIC-CTT[c]				X	X
EQ-5D-5L/ EQ-5D-Y[d]		X		X	X
HEOR assessments		X		X	X
AEs/SAEs	X	X	X	X	X
Vital sign measurements[e]	X	X	X	X	X
Complete physical examination[f]				X	X
12-Lead ECG				X	X
Urine pregnancy test (women of childbearing potential only)	X	X	X	X	X
Standard clinical chemistry panel- Central Lab[g]	X	X	X	X	X
Lactate		X		X	X
Hematology, coagulation panel, urinalysis - Central Lab	X	X	X	X	X

Visit Time (Day/Week)	W108	W120	W132	W144/ EOS	EW
Visit Window (Days)	**±14**	**±14**	**±14**	**±14**	**-**
Visit Type	**oPt/HH[a]**	**oPt/ HH[a]**	**oPt/HH[a]**	**oPt**	**InPt**
AAV8 binding antibody IgG testing (ELISA)		X		X	X
Anti-G6Pase antibody assay		X		X	X
Liver Ultrasound[h]				X	X
SMBG[i]	X	X	X	X	X
CGM[j]	X	X	X	X	X
Assessment of prescribed cornstarch and cornstarch intake[k]	X	X	X	X	X
Assessment of prescribed diet and dietary intake[k]	X	X	X	X	X

[a] Phone calls should be conducted by the site study team. Phone calls on days of Home Health visits should be conducted with Home Health visits to ensure AE collection, concomitant medication review, and assessment of diet and cornstarch.

[b] In subjects ≥ 18 years of age, height will be assessed only at Week 144 and Early Withdrawal visits.

[c] The GSD FAD will be completed every morning and evening for 7 days before each applicable study visit. The PGIC and PGIS will be completed electronically via the eDiary on the day before the applicable study visit. If PGIC and/or PGIS data have not been reported in the eDiary preceding the applicable study visit, the clinic site staff will have the subject complete the PGIC and/or PGIS on paper at the time of the study visit. The PGIC-CTT will be completed on paper at the applicable postbaseline study visits.

[d] The EQ-5D-5L (or EQ-5D-Y for subjects < 18 years of age) will be completed on paper at the study visit before any invasive study assessments or procedures.

[e] Vital signs will include seated systolic blood pressure and diastolic blood pressure measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature in °C. Vital sign measurements will be performed before any additional assessments are completed, except on the day of IP infusion when they will be performed more frequently, as detailed in Section 9.1.4.

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[g] Standard clinical chemistry assessments required at each study visit are listed in Table 19. Samples for clinical chemistry should be collected after vital signs and other noninterventional assessments have been performed and at least 2 to 4 hours after the subject's last meal.

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[j] It is recommended that subjects wear the CGM device and connect to the study issued computer to transfer CGM transmitter data collection throughout the study. CGM device must be worn for at least 4 weeks prior to visits at Weeks 108, 120, 132 and 144/EOS.

[k] Subjects must record their cornstarch and diet intake in the eDiary before all scheduled visits. Subjects must record their cornstarch intake daily for at least 1 week prior to visits at Weeks 108, 120, 132, and 144/EOS. Subjects must record their daily diet for a full 3 days prior to visits at Weeks 108, 120, 132 and 144/EOS. All cornstarch and diet prescriptions will be recorded in EDC at Screening, Baseline, and all visits. Section 10.2.1 provides further details. The Investigator should review the CGM data and other data collected from the eDiary, EDC, and confirmatory exchanges with the subject at least once a week to manage the subject's prescribed cornstarch and diet regimen. Study endpoint analyses will use the SMBG, CGM, and cornstarch intake data from 1 week before each study visit, so preferably the prescribed regimen should not be changed within 2 weeks before a planned study visit. If a change to the cornstarch or diet regimen is necessary during that time, contact the Medical Monitor to discuss whether the planned study visit should be delayed. Section 7.1.2, Section 10.2.2 and Section 10.2.3 provide further details regarding cornstarch regimen modifications and SMBG and CGM procedures, respectively.

AAV8, adeno-associated virus serotype 8; ACTH, adrenocorticotropic hormone; AE, adverse event; CGM, continuous glucose monitoring; CRF, case report form; D, day; ECG, electrocardiogram; eDiary, electronic diary; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzymelinked immune absorbent spot; EOS, end of study; EQ-5D-(5L/Y), EuroQol- 5 Dimension (5-level/youth version); EW, early withdrawal; G6Pase, glucose-6-phosphatase (protein); GSD FAD, Glycogen Storage Disease Functional Assessment Diary; HEOR, health economics outcomes research; HH, home healthcare visit; IGFBP1, insulin like growth factor binding protein 1; InPt, inpatient visit; HPA, hypothalamic-pituitary-adrenal; IP, investigational product (DTX401 or placebo); oPt, outpatient visit; PGIC, Patient Global Impression of Change; PGIC, Patient Global Impression of Change – Cornstarch Treatment Tolerance; PGIS, Patient Global Impression of Severity; SAE, serious adverse event; SMBG, self-monitored blood glucose; W, week

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAV	adeno-associated virus
AAV8	adeno-associated virus serotype 8
ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic-Therapeutic-Chemical (class)
CFC	controlled fasting challenge
CGM	continuous glucose monitor(ing)
CIC	Central Independent Committee
CMH	Cochran-Mantel Haenszel
COVID-19	coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ddPCR	Droplet Digital polymerase chain reaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DMP	disease monitoring program
DRG	dorsal root ganglion
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
EQ-5D-(5L/Y)	EuroQol 5-Dimension (5-level/youth version)
FAS	Full Analysis Set
FDA	Food and Drug Administration
G6Pase	glucose-6-phosphatase (protein)
G6PC	glucose-6-phosphatase (gene)
G6pc-/-	glucose-6-phosphatase knockout mice

Abbreviation	Definition
GC	genome copies
GCP	good clinical practice
GLP	Good Laboratory Practice
GSD FAD	Glycogen Storage Disease Functional Assessment Diary
GSDIa	glycogen storage disease type Ia
HCA	hepatocellular adenoma
HCC	hepatocellular carcinoma
HCP	health care provider
HDL	high density lipoprotein
HEOR	health economics outcomes research
HPA	hypothalamic-pituitary-adrenal
HPQ	Health Productivity Questionnaire
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IFN-γ	interferon-gamma
IGFBP1	insulin like growth factor binding protein 1
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product (ie, DTX401 or placebo)
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent to treat
IV	intravenous
LDL	low density lipoprotein
LFT	liver function tests
L-G6pc$^{-/-}$	liver-specific glucose-6-phosphatase knockout mouse
LOS	length of stay
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MIM	Mendelian Inheritance in Man
MMRM	mixed model repeated measure
MRU	medical resource utilization
NOAEL	no observed adverse effect level

Abbreviation	Definition
OBD	optimal biologic dose
PEAP	Primary Efficacy Analysis Period
PGIC	Patient Global Impression of Change
PGIC-CTT	Patient Global Impression of Change – Cornstarch Treatment Tolerance
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PRO	patient-reported outcome
PT	preferred term
qPCR	quantitative polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SHE	severe hypoglycemic event
SMBG	self-monitoring blood glucose
SOC	system organ class
STAT	as quickly as possible
SUSAR	serious, unexpected, suspected adverse reactions
TAb	total antibody
TB	total bilirubin
TEAE	treatment-emergent adverse events
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
WHO	World Health Organization

Definition of Terms

Investigational Product (IP) is defined as, “A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use” (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] Harmonised Tripartite Guideline E6: Guideline for Good Clinical Practice [GCP]).

The term “study drug” may also be used in place of “investigational product (IP)” in the protocol.

5. INTRODUCTION

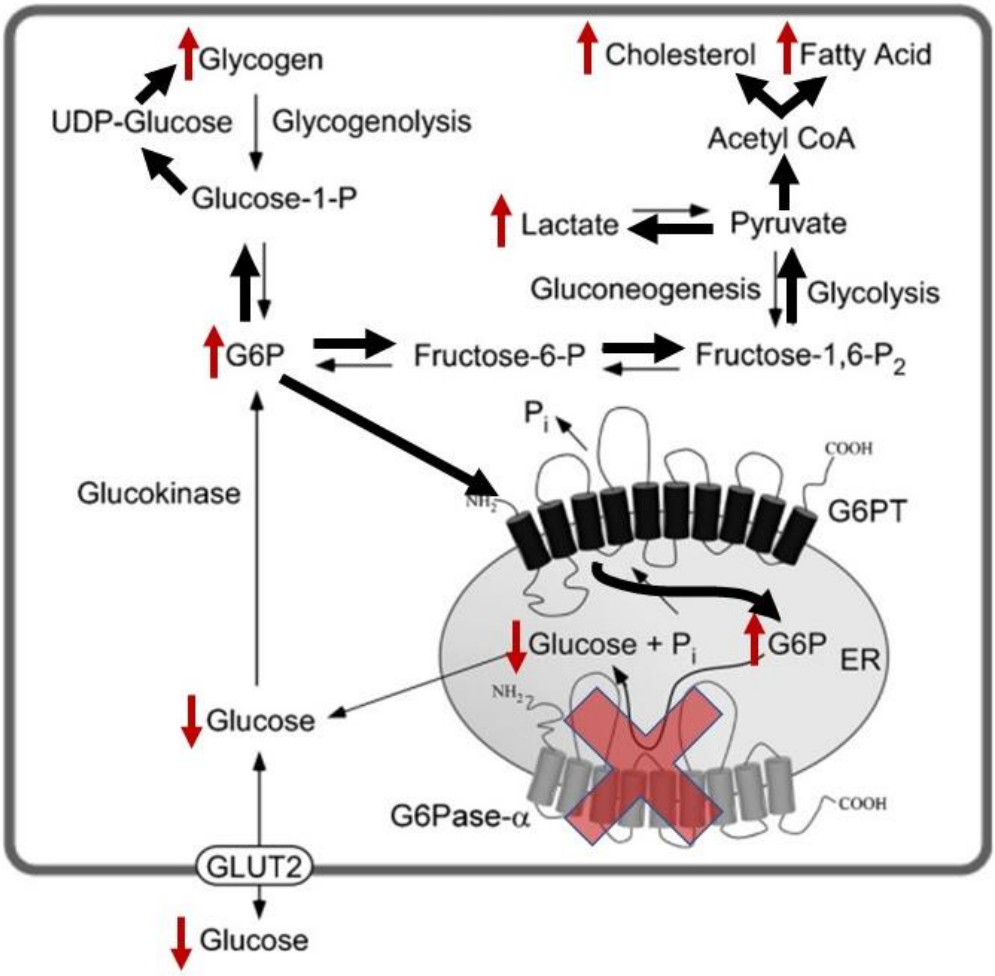
DTX401 is a gene therapy that is being developed for the treatment of glycogen storage disease type Ia (GSDIa). Patients with GSDIa have a deficiency in the glucose-6-phosphatase protein (G6Pase) enzyme and therefore cannot release glucose from glycogen storage in the liver during times of fasting (ie, during the period between meals) and are at risk for severe fasting hypoglycemia. DTX401 therapy is expected to provide G6Pase activity resulting in efficient release of glucose from glycogen stores in the liver, thereby reducing the risk of hypoglycemia during periods of fasting and the long-term complications associated with GSDIa.

The purpose of this study is to investigate the efficacy and safety of DTX401 in pediatric (8 to < 18 years) and adult (≥ 18 years) subjects with GSDIa.

5.1. Overview of GSDIa

GSDIa (MIM 232200) is a rare, serious, and potentially life-threatening disease caused by mutation of a single gene, *G6PC*, which encodes the G6Pase enzyme on chromosome 17q21 (OMIM, 2020). G6Pase is expressed primarily in the liver, as well as the kidney and intestine (OMIM, 2020; Chou, 2001; Lei et al., 1993) and is essential for the final step in the release of glucose from both the gluconeogenic and glycogenolysis pathways (Figure 2).

Figure 2: G6Pase-α Deficiency Leads to Hypoglycemia During Fasting



ER, endoplasmic reticulum; G6P, glucose-6-phosphate; G6Pase-α, glucose-6-phosphatase (protein)-alpha; G6PDH, glucose-6-phosphate dehydrogenase; G6PT, glucose-6-phosphate transporter; GLUT2, glucose transporter 2; HMS, hexose monophosphate shunt
Source: (Chou et al., 2015)

5.1.1. GSDIa Incidence, Diagnosis, and Complications

The estimated incidence of GSDIa is approximately 0.8 in 100,000 (NORD, 2019; AGSD, 2016). Diagnosis commonly occurs at 3 to 6 months of age, when patients present with hepatomegaly or symptomatic hypoglycemia after a short fast; however, some patients may present in the neonatal period with hypoglycemia and lactic acidosis (Kishnani et al., 2014; Chou et al., 2002). Additional clinical features of GSDIa may include doll face, stunted growth and hypotrophic muscles, diarrhea, hyperlipidemia, hyperuricemia, and impaired platelet function (Rake et al., 2002a; Rake et al., 2000). Most identified mutations are severe or null, resulting in little to no residual G6Pase enzymatic activity (Chou and Mansfield, 2008). The importance of diagnosing and treating GSDIa early is emphasized by the life-threatening complications that arise when the disease is left untreated.

Hypoglycemia in patients with GSDIa may be symptomatic but is frequently asymptomatic; in many instances, patients with GSDIa do not experience low glucose symptoms until blood glucose levels are dangerously low. If left untreated, hypoglycemia leads to seizures, coma, and death (Froissart et al., 2011; Rake et al., 2002a).

Long-term complications of GSDIa are related to the nutritional and metabolic consequences of abnormal glucose metabolism and the chronic build-up of glycogen stores and affect numerous body systems, including the liver, kidney, and bone (Franco et al., 2005; Chou et al., 2002; Rake et al., 2002a; Wolfsdorf and Crigler, 1997; Wolfsdorf et al., 1997).

Impaired growth and late-onset of puberty are commonly observed (Rake et al., 2002a). Patients with GSDIa may develop severe lactic acidosis, hyperlipidemia, microalbuminuria, proteinuria, anemia, hypertension, hyperuricemia, renal calcification, and progressive renal disease (Rake et al., 2002a; Rake et al., 2000; Weinstein et al., 2001). Renal dysfunction is detected in the majority of patients with GSDIa by the age of 19, and the incidence and severity of renal disease have been shown to increase with age (Labrune, 2002; Rake et al., 2002a).

Complications due to the pathological accumulation of glycogen in the liver, such as hepatomegaly and the formation of hepatocellular adenomas (HCAs) and hepatocellular carcinomas (HCCs), become more common as individuals with GSDIa age (Franco et al., 2005). HCAs are present in 70% to 80% of patients with GSDIa over the age of 25 years (Lee et al., 2012), with up to 10% of HCAs developing into life-threatening HCCs (Lee et al., 2012; Reddy et al., 2007; Franco et al., 2005). Importantly, HCAs may still occur even when patients with GSDIa are compliant with dietary restrictions and cornstarch use (Wang et al., 2011; Di Rocco et al., 2008).

Patients with GSDIa and their caregivers experience adverse effects on sleep and well-being. To maintain blood glucose levels in the normal range, patients ingest uncooked cornstarch approximately every 2 to 3 hours during the day and approximately every 4 hours overnight, which leads to daily disruption of daytime activities and sleep and may cause increased anxiety related to the ongoing complexities associated with metabolic management and the potential life-threatening consequences of mismanagement. This necessary preoccupation with diet in patients can also manifest in disordered eating behaviors, which could have significant or even fatal consequences for individuals with GSDIa (Flanagan et al., 2015).

5.1.2. Current Standard of Care for GSDIa

There is no available cure for GSDIa, and no approved therapies directly target the underlying cause of the disease. Current management consists of rigorous dietary control and avoidance of fasting. The primary goal of managing patients with GSDIa is to maintain serum glucose levels in the normal range throughout the day and night to avoid hypoglycemia (Ross et al., 2020; Kishnani et al., 2014; Froissart et al., 2011; Rake et al., 2002b). Management consists of rigorous dietary control and avoidance of fasting and includes the following:

- Frequent monitoring of blood glucose levels.
- Strict dietary restrictions to avoid simple sugars.

- Frequent consumption of uncooked cornstarch or Glycosade (a modified longer-acting cornstarch) and, if needed, continuous glucose feeds to prevent hypoglycemia and maintain metabolic control.
- Medications to manage the long-term complications associated with GSDIa.
- Dietary supplements to prevent or treat nutrient deficiencies.
- Liver transplantation may be a treatment option for patients with GSDIa. Liver transplant surgery is associated with significant short-term risks, is limited by donor availability and compatibility, and requires lifelong immunosuppression.

Although uncooked cornstarch has been the mainstay of GSDIa treatment, it is a crude method to control glucose, often allowing wide fluctuations in blood glucose levels; does not normalize the overall health of the patients; and may contribute to the risk of metabolic syndrome (Melis et al., 2015).

5.1.2.1. Dietary Restrictions and Cornstarch Consumption

Dietary restrictions for patients with GSDIa include avoidance of simple sugars such as glucose, fructose, galactose, lactose, and sucrose (Kishnani et al., 2014), which raise insulin levels and cause rapid uptake of glucose by the cells, leading to rebound hypoglycemia. To avoid hypoglycemia, patients ingest uncooked cornstarch approximately every 2 to 3 hours during the day and approximately every 4 hours overnight, which leads to daily disruption of daytime activities and, importantly, sleep. Cornstarch is digested slowly and provides a steady release of glucose and more stable glucose levels over a longer period of time compared to other sources of carbohydrates (Kishnani et al., 2014). However, glucose replacement with cornstarch is imprecise and unresponsive to physiologic changes, leading to wide fluctuations in glucose levels and periods of hyperglycemia and hypoglycemia. Many patients also find cornstarch unpalatable and experience gastrointestinal symptoms, such as bloating, flatulence, and diarrhea (Kishnani et al., 2014; Rake et al., 2002a). Glycosade, a modified cornstarch product, is available for overnight use (Kishnani et al., 2014). However, Glycosade is also associated with significant gastrointestinal distress (Bhattacharya, 2015) and is not indicated in children < 5 years of age. Oral cornstarch taken frequently, including in the evening and the middle of the night, can save patients but is not by any means a sufficient treatment for GSDIa.

5.1.2.2. Medications and Dietary Supplements

Medications may be prescribed to manage the long-term complications associated with GSDIa (Martens et al., 2009; Bandsma et al., 2008; Melis et al., 2005) but they are frequently associated with side effects. Lipid-lowering drugs, such as fibrates, may decrease triglyceride levels in patients with GSDIa (Bandsma et al., 2008). Angiotensin-converting enzyme inhibitors, such as captopril, are used to treat renal dysfunction and microalbuminuria, an early indicator of renal impairment in patients with GSDIa (Martens et al., 2009; Melis et al., 2005). Potassium citrate supplements may be used to treat hypocitraturia in patients with GSDIa (Weinstein et al., 2001) and allopurinol may be used to treat hyperuricemia.

5.1.2.3. Liver Transplantation

Liver transplantation is a treatment option for patients with GSDIa and has been shown to correct hypoglycemia and other biochemical abnormalities associated with GSDIa (Matern et al., 1999). However, liver transplant surgery is associated with significant short-term risks (including acute rejection, death, perioperative bleeding, infection, and other complications) and a high rate of renal failure (Boers et al., 2014; Davis and Weinstein, 2008). Liver transplant is also limited by donor availability and compatibility and requires lifelong immunosuppression. Complications associated with immunosuppression after liver transplantation include toxicity, hypertension, reversible insulin-dependent diabetes, and development of malignancies (Boers et al., 2014).

5.1.3. Unmet Medical Need

Patients with GSDIa whose disease is managed by strict nutritional regimens and adjunct drug therapies face a substantial burden of disease and unmet medical need. These burdens include the following:

- **Lifelong dietary and glucose monitoring regimens:** Monitoring blood glucose levels and maintaining dietary feeding and restrictions requires constant vigilance. Multiple cornstarch feedings during the day are a burden on daily activities, and those at night are detrimental to sleep. In addition, cornstarch may be unpalatable and can cause gastrointestinal symptoms, which may contribute to reduced compliance.
- **Hypoglycemia:** Life-threatening hypoglycemia is a risk that can occur with a single missed dose or even a delayed dose of cornstarch. Even with optimal metabolic control, patients remain at risk for severe hypoglycemia and death due to lapses in dietary compliance, such as in the setting of a patient or parent sleeping through a clock alarm and missing a single dose of cornstarch. A retrospective analysis revealed that more than one third of GSDIa patients experienced episodes of coma (Rake et al., 2002a). In an online survey sponsored by Ultragenyx, all patients reported experiencing a hypoglycemic event despite not missing a cornstarch dose (Butler et al., 2020). Periods of hyperglycemia also occur because the cornstarch dose is intended to keep glucose elevated for several hours. This might contribute to the risk of chronic hyperinsulinemia and metabolic syndrome (Melis et al., 2015). Thus, the lack of precision of glucose replacement is a complex problem despite the best most compliant patient regimen. Because the quality of glycemic control is correlated with long-term outcomes, the daily periods of hypoglycemia represent a measurable unmet need.
- **Health-related quality-of-life impact:** Health-related quality of life is affected by the disease itself, its complications, and the strict dietary requirements. The effects include interruptions to nightly sleep and daytime activities, changes in physical appearance (eg, height, weight, body shape), and psychosocial consequences. In initial survey results from a comprehensive assessment of the impact of GSDIa on health-related quality of life, hypoglycemic events and dietary restrictions were identified as the most important aspects of GSDIa to improve with a potential treatment.

- **Long-term complications:** Some laboratory abnormalities improve with dietary compliance, but hypercholesterolemia, hypertriglyceridemia, and hyperuricemia remain prevalent. Patients also continue to be at risk for increased morbidity and mortality from long-term complications such as renal disease, osteopenia, anemia, hepatic adenomas, and hepatic carcinoma.

5.2. Overview of DTX401 Development

A brief overview of existing information on DTX401 is provided below; a comprehensive review of available data is available in the Investigator's Brochure (IB) provided by Ultragenyx, which should be reviewed before initiating the study.

5.2.1. Brief Description of DTX401

DTX401 is a nonreplicating, recombinant, adeno-associated virus (AAV) serotype 8 (AAV8) vector for the treatment of GSDIa. The DTX401 vector genome contains a codon-optimized wild-type human *G6PC* and native human *G6PC* promoter and enhancer elements. The presence of the native promoter allows the transgene to be regulated by physiologic signals of glucose control. DTX401 is designed to deliver the *G6PC* transgene to hepatocytes, resulting in the production of normally functioning G6Pase enzyme.

Ultragenyx is developing DTX401, a single-administration gene therapy product, to directly treat the underlying cause of GSDIa. DTX401 has strong tropism for the liver and is designed to deliver human *G6PC* to hepatocytes, resulting in the production of normally functioning G6Pase. DTX401 includes about 3 kilobases of the normal promoter region for the *G6PC* gene, which provides the transgene with the ability to respond to physiologic signals related to glucose control including steroids (induced), glucagon (induced), and insulin (repressed). This feature enables the transgene to be regulated as if it were the endogenous gene, allowing for correct regulation in response to stimuli in vivo.

5.2.2. Nonclinical Studies

Ultragenyx has conducted a comprehensive nonclinical program to support the IV administration of DTX401. The nonclinical program for DTX401 includes assessments of potential efficacy, biodistribution, and toxicity in animal models of GSDIa and in wild-type C57BL/6 mice.

The pharmacology of DTX401 has been assessed in a series of non-Good Laboratory Practice (non-GLP) pharmacology studies. These studies supported selection of an AAV8 vector containing a codon-optimized version of the human *G6PC* gene for clinical candidate (DTX401) development and identified the minimal efficacious dose in mice, which was used to determine the clinical starting dose.

The safety and biodistribution of DTX401 were assessed as part of a GLP 92-day biodistribution and toxicology study (CCI) in C57BL/6N mice. Following a single IV dose of DTX401, vector genome DNA and hG6PC mRNA were found in the blood and were distributed ubiquitously throughout the body, with the highest level found in the liver and persisting until the end of the study (Day 92), confirming the hepatotropism of the AAV8 vector. DTX401-related findings included an expected AAV8 capsid immune response (anti-AAV8 neutralizing antibodies; interferon-gamma [IFN-γ] T-cell response), as well as changes in hematology and

clinical chemistry that were almost completely reversible by Day 92. Lymphoid hyperplasia in the spleen and lymph nodes and single cell necrosis/apoptosis with Kupffer cell hypertrophy/hyperplasia in the liver was observed at the highest dose (6.5×10^{13} genome copies per kilogram [GC/kg], with the vector genome titer measured by quantitative polymerase chain reaction [qPCR]) and showed reversibility by Day 92. Liver findings were considered adverse; therefore, the no observed adverse effect level (NOAEL) was determined to be the mid-dose (1.0×10^{13} GC/kg). The NOAEL from this study provides a ≥ 17-fold safety margin to the highest clinical dose of 6×10^{12} GC/kg (per qPCR), based on allometric scaling.

A germline transmission study (Study CCI) with CCI an Ultragenyx gene therapy product with an AAV8 vector similar to DTX401 (CCI), has been conducted to fulfill the developmental and reproductive toxicity assessment of DTX401. This germline transmission study in C57BL/6N mice following a single IV dose of CCI demonstrated the absence of any germline transmission to offspring. Additionally, no CCI effects on fertility or pregnancy outcomes were observed in CCI male or female animals.

A weight-of-evidence–based tumorigenicity and carcinogenicity risk assessment was conducted for DTX401. A thorough review of the literature failed to show a significant correlation between AAV integration and HCA or HCC formation and indicated that the risk of tumorigenicity/carcinogenicity is low. Results from an investigative toxicology study conducted with CCI to characterize the potential for AAV integration and risk of HCC formation (Study CCI) in *spf*^{ash} and C57BL/6N mice did not demonstrate an increased risk of tumorigenicity or vector integration leading to HCC formation with CCI administration.

5.2.3. Previous Clinical Studies

DTX401 is being developed for the treatment of adult and pediatric patients with GSDIa. The clinical development program includes 2 clinical studies in adults: a Phase 1/2 study (401GSDIA01) and a follow-up extension study (401GSDIA02).

Study 401GSDIA01 is a completed Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study in adult subjects ≥ 18 years of age with GSDIa. Subjects received a single intravenous (IV) infusion of DTX401 (vector genome titer was measured using a quantitative polymerase chain reaction method). A per-protocol reactive corticosteroid regimen with an 8-week taper was administered to treat vector-induced hepatic effects. The DTX401 dose level and concomitant corticosteroid regimen for each cohort are shown in Table 6. Corticosteroid regimens could be extended as clinically appropriate.

Table 6: DTX401 Dose Level and Concomitant Corticosteroid Regimen by Cohort (Study 401GSDIA01)

Cohort	DTX401 Dose Level[a]	Corticosteroid Regimen (Prednisone)[b]
Cohort 1 (n = 3)	2.0×10^{12} GC/kg	Reactive corticosteroids (6 weeks, starting dose of 40 mg/day, after ALT elevation)
Cohort 2 (n = 3)	6.0×10^{12} GC/kg	Reactive corticosteroids (6 weeks, starting dose of 40 mg/day, after ALT elevation)
Cohort 3 (n = 3)	6.0×10^{12} GC/kg	Optimized reactive corticosteroids (7 weeks, starting dose of 60 mg/day, after ALT elevation)
Cohort 4 (n = 3)	6.0×10^{12} GC/kg	Prophylactic corticosteroids[c] (8 weeks, starting dose of 60 mg/day, starting on Day 1)

[a] Vector genome titer measured using a quantitative polymerase chain reaction method
[b] Total duration of corticosteroid treatment including taper
[c] Two subjects in Cohort 4 received prednisolone
ALT, alanine aminotransferase; GC, genome copies

The last patient, last visit for this study occurred in November 2021. Results from all 12 subjects in the Phase 1/2 401GSDIA01 study provide evidence of restored G6Pase enzymatic activity. In this first-in-human study, delivery of G6PC to hepatocytes within an AAV8 vector (DTX401) had a consistent safety profile across all dose cohorts, with no dose limiting toxicity, treatment emergent adverse event (TEAE) leading to study discontinuation, TEAE leading to death, serious treatment-related TEAE or Grade 4 (life-threatening) SAE. Prophylactic and reactive use of oral steroids mitigated the important potential risk of vector-induced hepatic effects. A single IV infusion of DTX401 was associated with maintained or improved glycemic stability through 52 weeks, despite persistent reduction in average daily cornstarch needs (both frequency and volume). Times to hypoglycemia in a controlled fasting challenge were more variable, due in part to changing requirements for the prefasting meal and cornstarch intake during the study, to mitigate possible hormonal influences (high post-prandial insulin) and inappropriate cortisol responses to low glycemic values, as well as variations in steroid use. Most patients reported improvement in health-related quality of life and everyday activities. All 12 subjects from the Study 401GSDIA01 have enrolled into an ongoing long-term safety and efficacy study, 401GSDIA02. Study 401GSDIA02 is a follow-up extension study; only subjects who received DTX401 in Study 401GSDIA01 are eligible to participate. With participation in both studies, subjects are followed for at least 5 years after receiving DTX401.

Safety data from Studies 401GSDIA01 and 401GSDIA02 (data cutoff 19 April 2023) showed that of the 29 SAEs reported through the data lock point, most were Grade 2 in severity (n=21; 72%). No subject experienced a DTX401-related SAE, and no deaths occurred. There were four Grade 4 (life-threatening) SAEs reported from Study 401GSDIA02, including 3 events of gastroenteritis and 1 event of multiple organ dysfunction syndrome, which were assessed by the Investigator and Sponsor as not related to DTX401. The events of gastroenteritis were attributable to viral etiology and occurred over 2 years after DTX401 administration. The event of multiple organ dysfunction occurred in the setting of septic shock secondary to cholecystitis with event onset 3 years after DTX401 administration. As of the data cutoff, all SAEs were reported as resolved (n=27) or resolved with sequelae (n=2). Thus, the cumulative data from studies 401GSDIA01 and 401GSDIA02 support further clinical study in subjects with GSDIa.

5.3. Rationale for DTX401 in GSDIa

Based on the mechanism of action and the Phase 1/2 clinical study results, DTX401 therapy is expected to provide G6Pase activity resulting in efficient release of glucose from glycogen stores in the liver, thereby reducing the risk of hypoglycemia during periods of fasting and the long-term complications associated with GSDIa.

5.4. Potential Risks and Benefits

Due to the limited clinical experience with DTX401, all SAEs considered related to DTX401 are considered serious, unexpected, suspected adverse reactions (SUSARs) and are reported immediately. As of the data cutoff of 19 April 2023, no subject experienced a DTX401 hepatic-related SAE. Expected elevations in liver enzymes in response to the transgene in most subjects were treated with a tapering course of steroids. The most common product-related AE observed in human clinical studies with AAV-mediated gene transfer has been an asymptomatic transient rise in liver aminotransferases (without clinical sequelae) and a concurrent decrease in transgene expression approximately 7 to 10 weeks after vector administration. Vector-induced hepatic effects (eg, increased aminotransferase levels) in response to AAV administration have been identified as an important potential risk and are considered an adverse event of special interest (AESI) for DTX401.

Potential vector-induced hepatic effects of DTX401 are currently managed with prophylactic corticosteroids, and additional oral corticosteroids may be administered following completion of the prophylactic corticosteroid regimen (Section 9.2). Prednisolone is a corticosteroid with immunosuppressive properties. Treatment with prednisolone is associated with risks including fluid retention, altered glucose tolerance, weight gain, hypothalamic-pituitary-adrenal (HPA) axis suppression, infections, hypertension, behavioral/mood disturbances, decreased bone density. Risks associated with prednisolone treatment will be monitored by the Investigator during study visits and phone calls to subjects at the time of the prednisolone/placebo regimen. Adrenal insufficiency is considered a potential risk of study-related procedures and is an AESI.

Because corticosteroid administration increases the risk of immunosuppression, patient vaccination schedules will be adjusted such that they do not overlap with corticosteroid treatment, when feasible. Certain vaccines, such as measles, mumps, and rubella (MMR) and varicella, which are live vaccines, are contraindicated for patients on a substantially immunosuppressive steroid dose for more than 14 days. Investigators should time the administration of any vaccine to be at least 1 month before administration of blinded IP, or to be after completion of the 8-week regimen, considering that the highest dose is 60 mg/day or 1 mg/kg/day, depending on weight, for 4 weeks, followed by a 4-week taper regimen (Section 9.2.1).

Infusion-related reactions (IRRs) including hypersensitivity have been identified as an important potential risk and AESI for DTX401. IRRs with features of hypersensitivity have been observed with blinded IP in this trial, including anaphylaxis. IRRs for this study are defined as adverse events with features of hypersensitivity with onset during the infusion or up to 6 hours after end of the infusion.

IRRs may be allergic (anaphylactic) and mediated by IgE or may be nonallergic and not mediated by IgE. Regardless of whether they are allergic or nonallergic, the clinical

manifestations may be similar and require prompt, accurate assessment and astute management to avoid severe outcomes (Vogel, 2010). Symptoms of IRRs range from mild to severe or life-threatening and may include headache, myalgia, pruritis, urticaria, fever, flushing, diaphoresis, gastrointestinal symptoms (abdominal pain or cramping, vomiting), bronchospasm, hypotension, angioedema and anaphylaxis.

Potential IRRs are managed with predmedication, slow and staged infusion of blinded IP with close and continuous monitoring for infusion reactions by clinical staff experienced in management of infusion-related reactions and subject and parent/guardian education on signs and symptoms of allergic reactions at discharge. Refer to Section 5.5 for risk minimization for possible infusion reactions and Section 9.1.4 for clinical observation and supportive care.

Dorsal root ganglion (DRG) and peripheral nerve pathologies have been reported in nonhuman primates, piglets, and mice administered recombinant AAV gene therapy products (Bolt et al., 2021; Van Alstyne et al., 2021; Hordeaux et al., 2020a; Hordeaux et al., 2020b; Hinderer et al., 2018; Schuster et al., 2014).The clinical relevance and translation of these nonclinical DRG and nerve pathologies is not known.

The totality of the available literature information combined with the planned clinical dose (1.0×10^{13} GC/kg), use of a liver-specific promoter, and IV route of administration, suggests that the risk of DRG and peripheral nerve-related toxicities occurring with DTX401 treatment is low. Regardless, due to the possibility of transient or permanent DRG and peripheral nerve pathology from AAV treatment, study participants will be assessed regularly (at every outpatient and inpatient visit) for any safety events including sensory neuropathy symptoms. If such symptoms are identified, they will be recorded as adverse events and followed by a thorough neurological examination and additional nerve conduction and imaging studies as needed. In addition to this continuous safety monitoring, a complete physical examination, including systematic neurological examinations, will be conducted at Baseline, Week 48, Week 96, and Week 144/end of study (EOS) visit or Early Withdrawal visit.

Other DTX401 AAV8 vector-related safety risks are expected to be immune related and include the development of antibodies to AAV8, thus precluding the use of other AAV8 gene therapy products.

The mechanism of action of DTX401 is to deliver the *G6PC* gene to hepatocytes, resulting in the production of normally functioning G6Pase under the control of the normal endogenous regulatory promoter, thereby providing circulating glucose when glucose levels are low and resulting in a physiological response to regulatory signals for increased or decreased enzyme needs.

Unlike the current disease management approach that uses imprecise oral cornstarch and dietary control, DTX401 is designed to correct the underlying cause of GSDIa. The potential for significant clinical benefit has been seen in the Phase 1/2 study (Section 5.2.3). By reducing the required amount and frequency of cornstarch intake while maintaining or improving the target blood glucose range and extending the time to hypoglycemia in some patients to be close to the normal range, DTX401 has the potential to relieve the substantial burden of GSDIa related to constant dietary vigilance. Cornstarch reduction has also been associated with improved health -related quality of life, and the amount of cornstarch needed is a direct measure of this impact. Phase 1/2 subjects reported that reduction in cornstarch provides major clinical benefit to

their lives, with less fear of hypoglycemia, less volume to ingest, an ability to lose excess body weight, and an ability to travel or go through the day without carrying cornstarch and water. These perceptions have been confirmed in narratives by the corresponding Investigators, who perceive cornstarch reduction as a measure of functional glucose control that has a direct impact on the subjects' glycemic management.

Additional anticipated benefits of DTX401 include improvement in metabolic parameters and patients' health-related quality of life and prevention of long-term complications of GSDIa.

Overall, the primary endpoint and the complementary secondary endpoints in the Phase 3 study will enable a thorough evaluation of subject outcomes for all key features of GSDIa. We anticipate that the results are likely to provide evidence in favor of DTX401 as a clinically meaningful and effective therapy that addresses the root cause of GSDIa in pediatric and adult patients. Taking into account measures to minimize risk to participants in this study, the potential risks identified in association with DTX401 are justified by the anticipated benefits that may be afforded to participants with GSDIa.

5.5. Risk Minimization

In this study, the potential AAV-related risk of elevated liver function tests is addressed by a prophylactic corticosteroid taper for subjects who receive DTX401. The use of steroids in AAV gene therapy has been shown to be essential in managing liver inflammation, and there is increasing evidence that prophylactic steroids may be more effective than a reactive steroid regimen at reducing the intensity of vector-induced hepatitis and increasing the overall efficacy of AAV gene therapy.

Investigators will educate subjects on risks of prednisolone and the importance in adherence to the prednisolone/placebo regimen and reporting of any undesirable effects. Investigators should avoid a rapid taper of prednisolone/placebo outside of the recommended regimen (Section 9.2). Any changes from the recommended prednisolone/placebo regimen or restarting of a further prednisolone/placebo regimen should be discussed with the unblinded medical monitor and the Central Independent Committee (CIC). Investigators will call subjects during the steroid tapering regimen to monitor for symptoms or signs of iatrogenic Cushing's syndrome and adrenal insufficiency. Suspicion of adrenal insufficiency should warrant endocrinology consultation and stress dose steroids. An early morning cortisol and ACTH should be obtained 24 hours after completing the prednisolone/placebo taper. The CIC will review abnormal early morning cortisol and ACTH levels obtained 24 hours after completing the prednisolone/placebo taper.

Investigators will closely monitor subjects and will consider using stress dose steroids during acute illness, trauma or surgical procedures for subjects who have completed steroid treatment within the past 12 months, especially those who have low morning cortisol. HPA axis recovery testing and/or stress dose steroids will be considered if suppression of the HPA axis is suspected. Intramuscular (IM) or IV preparations of stress-dose corticosteroids should be considered where a subject is vomiting with likely poor gastrointestinal absorption.

Although the risk for vertical transmission of the AAV vector is low and a recent nonclinical study demonstrated the absence of any germline transmission with an Ultragenyx gene therapy product with an AAV8 vector similar to DTX401 (Section 5.2.2), females of childbearing potential and male subjects who are sexually active with female partners of childbearing

potential will be required to use an effective method of contraception throughout the full study and, in case of early withdrawal, for at least 48 weeks after the last dose of IP (Appendix 3 provides details regarding contraception).

To minimize risk to study subjects during infusion of blinded IP, clinical staff experienced in the management of infusion reactions and anaphylaxis must be available during the infusions. Medications to treat anaphylaxis (antihistamines, steroids, epinephrine, glucagon, oxygen, and IV fluids) must be available at subject's bedside in the event of an allergic reaction. Subjects will be premedicated 30 to 60 minutes prior to the start of blinded IP infusion with acetaminophen/paracetamol, 2nd generation H1 antagonist (eg, cetirizine, loratadine, fexofenadine) and an H2 antagonist (eg, famotidine). Subjects will be administered blinded IP slowly per infusion rates specified in the Pharmacy Manual. Subjects will be monitored closely for infusion reactions for at least 6 hours after administration of the IP (Section 9.1.4). Study site staff will provide subjects and/or their parents or guardians with instructions to monitor for signs and symptoms of allergic reactions and when to seek emergency medical treatment after discharge.

Subjects will be closely monitored for safety throughout the study, including during periods of adjustment to modified cornstarch treatment. The CIC will review SMBG, CGM, and cornstarch intake data routinely throughout the study to provide guidance on cornstarch management to Investigators for both treatment groups to safeguard the blind (Section 11.7). The ultimate decision to reduce cornstarch intake and/or the rate of reduction will be each Investigator's responsibility, taking into account each subject's clinical status and overall safety.

An independent Data Monitoring Committee (DMC) will act in an advisory capacity to monitor subject safety on a routine basis throughout the course of the study, as described in Section 11.7.

Upon completion of this study (EOS or Early Withdrawal), all subjects who receive DTX401 will be asked to enroll in a long-term follow-up study (GSDIa Disease Monitoring Program [DMP]) to evaluate the long-term safety and effectiveness of DTX401 for at least 10 years after DTX401 administration. The DMP for GSDIa will be conducted under a separate protocol.

6. OBJECTIVES AND ENDPOINTS

Table 7: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of DTX401 to reduce or eliminate dependence on exogenous glucose replacement therapy needed to maintain glucose control	• Percent change from Baseline to Week 48 in daily cornstarch intake for the DTX401 Group compared with the Placebo Group
Secondary (subject to multiplicity)	
To evaluate the effect of DTX401 on reducing the frequency of exogenous glucose replacement therapy	• Change from Baseline to Week 48 in number of total daily doses of cornstarch
To evaluate the effect of DTX401 on glucose control	• Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (<70 mg/dL [3.9 mmol/L]), assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority
To evaluate the effect of DTX401 on subject experience of disease	• PGIC assessment score at Week 48
Secondary (not subject to multiplicity)	
To evaluate the effect of DTX401 on glucose control	• Change from Baseline to Week 48 in time to hypoglycemia (<54 mg/dL [3.0 mmol/L]) during the CFC • Change from Baseline to Week 48 in percentage of glucose values in the range of 70-120 mg/dL (3.9-6.7 mmol/L), assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority
To evaluate the safety of DTX401	• Incidence, severity, and relationship to investigational product of TEAEs, TEAEs of special interest, serious TEAEs, related TEAEs, discontinuations from study or investigational product due to AEs, and fatal AEs

Objectives	Endpoints
Tertiary	
To explore the effect of DTX401 on additional parameters of metabolic control	• Change from Baseline to Week 48 (DTX401 vs placebo) in the following parameters: – Total number of hypoglycemic events (<54 mg/dL) in the 4 weeks prior to the visit based on CGM data. A hypoglycemic event is defined as at least 2 sensor values < 54 mg/dL that are at least 15 minutes apart with no intervening values >54 mg/dL. The end of the hypoglycemic event is defined as 2 sensor values > 70 mg/dL that are at least 15 minutes apart with no intervening values < 70 mg/dL. – Total duration of hypoglycemic events in the 4 weeks prior to the visit based on CGM data. – Time spent below 70 mg/dL (3.9 mmol/L) in the 4 weeks prior to the visit based on CGM data. – Observed overnight fasting time, based on PI assessment – Pre-CFC whole blood lactate – Plasma uric acid – Pre-CFC plasma alanine – Daily dietary (non-cornstarch) macronutrient intake (fat, protein, carbohydrates, and non-utilizable sugars) and percentage of total calories from individual macronutrients – Time between a glucose level of 70 mg/dL (3.9 mmol/L) to < 54 mg/dL (3.0 mmol/L) during the CFC • Percentage of subjects at Week 48 who do not require overnight cornstarch (overnight cornstarch is defined as any dose disrupting normal sleep patterns) • Percentage of subjects at Week 48 who do not require cornstarch during the day • Percentage of subjects with > 75% reduction in total daily cornstarch intake from Baseline to Week 48 (DTX401 vs placebo)
To explore the additional effect of DTX401 on subject experience of disease	• Change in GSD FAD Symptoms score(s) from Baseline to Week 48 • Change in the GSD FAD Impact score(s) from Baseline to Week 48 • Change in PGIS assessment score from Baseline to Week 48 • PGIC-CTT assessment score at Week 48 • Change in patient-reported health status via the EQ-5D-5L/ EQ-5D-Y instrument from Baseline to Week 48 • Change in MRU, specifically hospitalization and ER visits from Baseline to Week 48 • Change in work and school status and productivity, assessed via questionnaire and patient exit interviews from Baseline to Week 48 • Patient exit interviews

Objectives	Endpoints
To explore the precision and accuracy of CGM and SMBG in GSD1a patients	• Mean absolute relative difference (MARD) and bias of CGM relative to SMBG at all paired measurements • MARD and bias of CGM and SMBG relative to venous blood glucose during CFCs
To explore the hormonal and metabolic responses to fasting in the CFCs	• Characterization and change from baseline (as applicable) in the hormonal (ACTH, cortisol, IGFBP1, insulin, C-peptide) and metabolic (fatty acids, ketones, lactate, alanine) responses to fasting during the CFCs (DTX401 vs placebo)
To explore additional safety of DTX401	• Change from Baseline (DTX401 vs Placebo) in the following parameters: – eGFR, 24-hour urine protein, and urine protein-to-creatinine ratio – Hemoglobin, hematocrit, and platelets – Total bilirubin, ALT, AST, GGT, alkaline Phosphatase, albumin, INR – Heart rate, systolic and diastolic blood pressure, respiratory rate, weight (adults), weight Z-score (children), BMI (adults), BMI Z-score (children) – Triglycerides, Total cholesterol, LDL, and HDL • Presence and titer of anti-AAV8 antibodies • Presence and titer of anti-G6Pase antibodies • Cell-mediated response to AAV8 and G6Pase

AAV8, adeno-associated virus serotype 8; AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; BMI, body mass index; CFC, controlled fasting challenge; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; EQ-5D-(5L/Y), EuroQol- 5 Dimension (5-level/youth version); ER, emergency room; G6Pase, glucose-6-phosphatase; GGT, gamma-glutamyl transferase; GSD FAD, Glycogen Storage Disease Functional Assessment Diary; GSDIa, glycogen storage disease type Ia; INR, international normalized ratio; MARD, mean absolute relative difference; MRU, medical resource utilization; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; TEAE, treatment-emergent adverse event

7. INVESTIGATIONAL PLAN

7.1. Study Design

Study DTX401-CL301 is a Phase 3, randomized, double-blind, placebo-controlled study to determine the efficacy and confirm the safety of DTX401 in patients 8 years and older with GSDIa. Approximately 50 subjects will be enrolled and randomly assigned in a 1:1 ratio to receive DTX401 (n = 25) or placebo (n = 25). Approximately 20 subjects 8 to < 18 years of age will be enrolled. Randomization will be stratified by age (< 18 years vs ≥ 18 years) and Baseline percentage of values in the target blood glucose range (< 60%, ≥ 60% and ≤ 85%, > 85%).

7.1.1. Study Periods

This study includes the following sequential stages:

- **Screening (Day -122 to Day -10):** The site must obtain written informed consent for participation in the study before performing any study-specific screening tests or evaluations. (For pediatric subjects, a legal guardian must provide written informed consent, and the subject must provide age-appropriate assent to participate.) Section 8.5 provides additional details regarding subject consent/assent.

  All screening evaluations specified in Table 3 must be completed by the Investigator and reviewed to confirm that subjects meet all eligibility criteria.

  The subject/caregiver should be given the CGM system, a meter for capillary glucose measurements (ie, self-monitored blood glucose [SMBG]), and the electronic diary (eDiary) to start collecting baseline data immediately after signing the informed consent form (ICF; unless deemed ineligible by that time). Section 10.2.2 and Section 10.2.3 provide additional details.

  The Screening Period will be up to 112 days (16 weeks), depending on the duration of time needed to establish glycemic and cornstarch stability according to the following considerations.

  After the first week of screening, the Investigator and/or study dietitian will review the subject's current diet, cornstarch regimen, and glycemic control (assessed by both CGM and SMBG measurements) to determine if the subject requires nutrition modifications or if the subject's diet, cornstarch, and glycemic control are considered optimized (see "Nutrition Optimization Period" below). Nutritional management should be consistent with published guidelines (see Study Reference Manual and Appendix 1). If a subject does not require nutrition optimization, they may begin the 4-week stabilization period immediately.

  – **Nutrition Optimization Period:** The goal of nutrition optimization is to adjust cornstarch dosing and diet to minimize the occurrence of hypoglycemia and minimize elevations in lactate, triglycerides, and uric acid, while avoiding excessive cornstarch consumption, which can lead to obesity, hyperlipidemia, worsening hepatomegaly, and metabolic instability caused by hyperinsulinemia and rebound hypoglycemia. Nutrition education and close monitoring of diet,

cornstarch, and glycemic control will be provided according to nutritional guidelines (see Appendix 1). Once the Investigator and/or dietitian determine the subject has achieved nutritional optimization, the subject will begin the nutrition stabilization period.

– **Nutrition Stabilization Period:** All subjects must demonstrate at least 4 consecutive weeks of glycemic, diet, and cornstarch stability prior to randomization.

  - Glycemic stability is achieved if the percentage of values in the target blood glucose range (60-120 mg/dL) each week for the most recent 4 weeks is within 15 percentage points of the average of each of the 4 weeks as measured by CGM and corroborated by SMBG. If adequate corroboration between CGM and SMBG is not observed, SMBG should be used for assessment of glycemic stability.
  - Cornstarch stability is achieved if the average daily cornstarch intake each week for the most recent 4 weeks is within 10% of the average of each of the 4 weeks.
  - Diet (non-cornstarch carbohydrate) stability will be achieved if average grams of non-cornstarch carbohydrates from food and beverage each week for the most recent 4 weeks is within 25% of the average of each of the 4 weeks.

  Subjects will have up to 16 weeks from informed consent to complete nutrition optimization and stabilization.

The administration of IP will be delayed if a subject has had any vaccination, infection (febrile or nonfebrile) or disease flare within 1 month of scheduled IP administration.

- **Randomization Period (Day –10 to Day 0):** Screening ends when the subject is randomized. Using the interactive response technology (IRT) system, the site will randomly assign the subject to DTX401 or placebo treatment and schedule the investigational product (IP; ie, DTX401 or placebo) infusion at least 10 business days before the IP infusion date to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site. Investigators, site staff, subjects, and the Sponsor will be blinded to IRT treatment assignment. Once randomized, site staff must call the subject to complete assessments indicated in Table 3. During the period between Randomization and Baseline (Day 0), subjects must maintain cornstarch, diet, and glycemic stability. If cornstarch, diet, or glycemic stability is lost during this period, the Baseline Visit may be postponed (after discussion with the Sponsor and Medical Monitor) or the subject may be withdrawn from the study. Medical monitor approval is required to proceed to the Baseline Visit.
- **Baseline (Day 0):** The day before IP administration (ie, Day 0), the subject will be admitted to the hospital or a research facility for baseline assessments as specified in Table 3.
- **Day 1 IP Administration:** On Day 1, subjects randomly assigned to DTX401 will receive a single, blinded, peripheral IV infusion of DTX401 at 1.0×10^{13} GC/kg.

Subjects randomly assigned to placebo will receive a single, blinded, peripheral IV infusion of normal saline (Section 9.1.3).

- **Day 15:** Subjects randomly assigned to DTX401 will start an oral prophylactic prednisolone regimen to minimize or prevent potential vector-induced hepatic effects (eg, transaminase elevations). Subjects randomly assigned to placebo IP infusion will receive a matching oral placebo regimen to maintain the study blind. Site staff must call the subject to complete assessments indicated in Table 3 and remind them to initiate the prophylactic regimen.
- **The Primary Efficacy Analysis Period (PEAP; Day 1 to Week 48):** The PEAP is the time from Day 1 post-dose through the completion of the Week 48 controlled fasting challenge (CFC). The primary endpoint and secondary efficacy endpoints will be analyzed after the last enrolled subject completes the Week 48 assessments.
- **Week 48 IP Preparation:** Before scheduling the IP administration at Week 48, the Investigator should review all results from the Week 36 assessments as soon as they are available and assess the subject according to Study Continuation Criteria (Section 8.3) to confirm that the subject is able to receive IP administration at Week 48. If there is evidence of any other change from Baseline in disease status or overall well-being that would preclude safe administration of DTX401 at Week 48, the Medical Monitor should be consulted. The administration of IP will be delayed if a subject has had any vaccination, infection (febrile or nonfebrile) or disease flare within 1 month of scheduled IP administration.
    - It is possible that a subject who received placebo at Day 1 may not be able to receive DTX401 at Week 48 due to development of anti-AAV8 antibodies or due to another postbaseline change in disease status or overall health. In this case, the subject and the Investigator will be notified during the Week 48 Visit and the subject will withdraw from the study once all Week 48 assessments are completed.
    - The Week 48 IP administration must be scheduled in the IRT system at least 10 business days before the IP infusion date to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site.
- **Week 48 IP Administration:** At Week 48, after all Week 48 assessments are completed, subjects will receive a second blinded infusion of IP: subjects randomly assigned to DTX401 at Baseline will receive placebo at Week 48, while eligible subjects randomly assigned to placebo at Baseline will receive a single, blinded, peripheral IV infusion of DTX401 at 1.0×10^{13} GC/kg at Week 48 (if still eligible for IP infusion; see Section 8, Population).

  Refer to Section 9.1.3 for additional details regarding IP administration.

  Subjects will begin an oral prophylactic prednisolone regimen or matching oral placebo regimen (Section 9.2) 14 days after the Week 48 IP administration.
- **Holding Period (if required):** All Week 48 assessments must be complete prior to a subject entering into a Holding Period. The holding period consists of clinical or home health visits every 12 weeks as needed to allow continued follow-up of subjects

following the PEAP (eg, in the event of an unavoidable interruption to IP supply). Study Continuation Criteria (Section 8.3) will be reviewed prior to the second IP administration in the event of a prolonged Holding Period to confirm the subject is able to receive IP administration at Week 48. The AAV8 TAb assay should be repeated if more than 6 months have elapsed since the last measurement (i.e., in the unlikely event that a subject remains in a holding pattern for more than 6 months). If proceeding with the second IP administration, the timing of all subsequent visits and assessments (Table 4 and Table 5) should be anchored to the date of the second IP administration.

- **The Follow-up Period (Week 48 through Week 144):** Study assessments during the Follow-up Period will further characterize the efficacy and safety of DTX401 administration to inform the overall risk-benefit profile. The subjects, investigators, site study teams and a dedicated site-facing Sponsor study team will remain blinded until the last subject completes their Week 96 visit or early withdrawal visit.
- **Early Withdrawal (EW):** If a subject plans to leave or will be removed from the study, the subject will be requested to complete Early Withdrawal assessments as specified in Table 3.

Upon completion of this study (Week 144 or Early Withdrawal), all subjects who receive DTX401 will be asked to enroll in a long-term follow-up study (GSDIa DMP) to evaluate the safety and effectiveness of DTX401 via the DMP for at least 10 years after DTX401 administration.

7.1.2. Cornstarch Modification Guidance

The primary endpoint for this study is based on changes in subjects' daily cornstarch intake after IP administration. After treatment with DTX401, transgene expression and subsequent G6Pase activity can occur rapidly, resulting in the release of glucose from stored glycogen in the liver. If cornstarch levels are not adequately reduced, the combination of glucose from glycogen breakdown plus glucose from cornstarch and diet may result in hyperglycemia, triggering the release of insulin and rebound hypoglycemia; therefore, proper cornstarch management is essential for maintaining glycemic control.

Subjects should use the same brand of cornstarch throughout the study, as much as possible. If subjects use a mixture of Glycosade and cornstarch at baseline, the proportion of each should remain consistent, as much as possible, even as overall glucose levels from cornstarch and Glycosade ingestion are decreased. Exception to this rule is nighttime use of Glycosade that can be maintained as long as needed to achieve overnight glycemic control.

Modification to the dosage of baseline cornstarch treatment will be individualized and dependent on the clinical judgment of the Investigator after review of the available longitudinal clinical and laboratory data for each subject on discussion with the unblinded Medical Monitor, keeping subject safety as the first priority. Investigators will also consider additional guidance from the CIC regarding cornstarch regimen modification; the CIC will review SMBG and CGM recordings and cornstarch use/dietary intake data captured through the eDiary routinely throughout the study. Any changes to the cornstarch prescription will be recorded in the EDC.

Subjects will be given and will use a CGM system and capillary blood glucometer to assess their response to cornstarch changes as described in Section 10.2.2 and Section 10.2.3. Investigators will receive SMBG and CGM data for review to facilitate any modifications to the cornstarch regimen. During CFC, to maintain subject safety (if there is a sudden change in glucose levels), an additional CGM device offering real-time readings may be worn by the subject at the Investigator's discretion.

It is recommended the subject wears the CGM device throughout the study from Screening to Week 144. At minimum, subjects must wear the CGM device for at least 4 weeks prior to visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS. It is recommended that the subject collect at least 4 SMBG values daily over a 24-hour period from Screening through the Week 144 visit using capillary glucometer or as recommended by their Investigator in line with standard of care. At a minimum, SMBG must be performed at least 4 times a day in the 1-week period prior to visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS. Additional SMBG measurements may be performed when presenting with symptoms of hypoglycemia or hyperglycemia, or in any situation where there is an increased risk of hypoglycemia (eg, intercurrent illness, strenuous exercise, feeding difficulties, delayed meal) and also as instructed by the Investigator (eg when prolonged hypoglycemic events are recorded on CGM). The decision to adjust cornstarch should be based primarily on CGM trends and supported by SMBG values. Where SMBG and CGM data are not corroborated, modifications to cornstarch should be based on SMBG values.

The use of CGM in this study will provide the Investigator with 24-hour retrospective glucose levels, providing the Investigator with additional insights on glycemic trends and identifying values out of range that may require verification by additional SMBG testing.

Insights on glycemic control obtained by SMBG (with information on potential symptoms recorded in the eDiary) and CGM measurements, diet, and cornstarch data obtained via the eDiary and other clinical and laboratory data, will allow to safely adjust cornstarch intake to avoid hypoglycemia and hyperglycemia following the cornstarch management guideline.

If the CGM is malfunctioning or the subject cannot use the CGM for any other reason, the subject should alert the study site, which will coordinate CGM device repair or replacement.

Subjects will record actual cornstarch intake and dietary intake in an eDiary (Section 10.2.1). Additional assessments of glucose control or any other biomarker to assess subject safety and clinical status may be performed at the discretion of the Investigator and as clinically indicated. Please refer to Table 8 on recommendations for minimal collection of glycemic, diet, and cornstarch data for each study period.

Table 8: CGM, SMBG, Diet, and Cornstarch Data Collection Requirements

	Prior to dosing	After dosing
CGM	It is recommended that subjects wear the CGM device and connect to the study issued computer to transfer CGM transmitter data collection	• CGM device must be worn for at least 4 weeks prior to visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS • It is recommended that subjects wear the CGM device and connect to the study issued computer to transfer CGM transmitter data collection throughout the study as much as possible
SMBG[a]	Subjects must perform SMBG at least 4 times daily for at least 4 weeks before the Baseline Visit	• SMBG must be performed at least 4 times a day in the 1-week period prior to visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS • It is recommended that subjects perform 4 SMBG measurements per day or per Investigator's discretion in line with standard of care • SMBG measurements are recommended whenever hypoglycemia is suspected • Additional SMBG assessments may be performed at the discretion of the Investigator or if the subject is symptomatic[a]
Diet[a]	Daily[b]	• 3 consecutive days prior to visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS • Additional eDiary diet collection may be requested by the PI
Cornstarch[a]	Daily[b]	• Daily for 1 week prior to visits at Weeks 24, 30, 36, 42, 72, 78, 84, 90, 108, 120, 132 and 144/EOS and 4 weeks prior to visits at Weeks 48 and 96 • Additional eDiary cornstarch collection may be requested by the PI

[a] Diet and cornstarch are captured in the eDiary. Reasons for conducting SMBG if symptomatic should also be captured in the eDiary.
[b] Site staff should contact subjects to remind them when to begin daily eDiary entries.
CGM, continuous glucose monitoring; SMBG, self-monitoring blood glucose

7.1.2.1. Modifications to Prescribed Cornstarch Therapy

Investigators will review SMBG and CGM data from subjects provided to them in a weekly report to consider whether modifications to dietary and cornstarch prescriptions are warranted. Dietary and cornstarch compliance, other clinical and safety parameters, and laboratory results will also be taken into consideration when modifying cornstarch prescriptions.

Modifications to cornstarch dosage should be primarily based on the subject's last 7 days of CGM trends and supported by SMBG values. Where SMBG and CGM data are not corroborated, modifications to cornstarch should be based on SMBG values. Observations over the last

4 weeks should also be considered, and changes should be avoided, as noted below, in the 2 weeks immediately preceding any visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS.

Guidelines for adjustment to the cornstarch prescription include:

- The ultimate decision to reduce or increase cornstarch intake and/or the rate of reduction will be each Investigator's responsibility, taking into account each subject's clinical status and overall safety and based on the totality of glycemic, nutritional, cornstarch intake, clinical and safety data
- The Investigator should review the SMBG and CGM data, eDiary data, comparison of actual to prescribed diet and cornstarch information, central and local laboratory data, and confirmatory exchanges with the subject at least once a week to manage the subject's prescribed cornstarch and diet regimen
- Decrease cornstarch intake by a target of -10% of total intake if glucose peak levels are repeatedly ≥110 mg/dL (6.1 mmol/L) and low values are ≥ 80 mg/dL (4.4 mmol/L) more than 15% of the time compared to the previous dose for at least 3 days in a 1 week period.
- Increase cornstarch intake by a target of +10% if peak glucose values are <90 mg/dL (5.0 mmol/L) and low values are < 60 mg/dL (3.3 mmol/L) more than 15% of the time compared to the previous dose for at least 3 days in a 1-week period.
- During periods of cornstarch adjustment (eg in preparation of an inpatient visit, during steroid/placebo steroid exposure), subjects will be closely monitored. The date and reason for any modification to the prescribed cornstarch regimen will be entered on the case report form (CRF) including the reason for discrepancies between prescribed and actual cornstarch dosing and if needed how these discrepancies are being mitigated (eg nutrition counseling, change in prescription).

Study endpoint analyses will use the SMBG, CGM, and cornstarch intake data from weeks leading up to each study visit; therefore, the prescribed regimen should not be changed within 2 weeks before any visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS. If a change to the cornstarch or diet regimen is necessary during that time (eg, due to intercurrent illness), or if for any reason the subject was unable to record cornstarch, diet, SMBG, and CGM during that time the Medical Monitor should be contacted to discuss whether the planned study visit should be delayed.

During the Screening Period, the same guidance may be applied by Investigators to optimize and stabilize cornstarch and diet and obtain the best glycemic control prior to dosing.

The unblinded Medical Monitor, and if needed, the CIC, will review SMBG, CGM and cornstarch intake data for both treatment arms routinely throughout the study and the CIC will provide per protocol guidance on cornstarch management to Investigators (Section 11.7) or address questions and requests for alternative cornstarch management choices (that will require written justification for CIC's review).

7.1.2.2. Reinstitution of Cornstarch Therapy

Subjects' glucose levels may stabilize to the point where cornstarch intake is no longer required, and cornstarch therapy may be discontinued. However, the Investigator must still monitor glucose levels closely. At any time after discontinuation, cornstarch therapy may be resumed, at the subject's last prescribed regimen or to a dose that the Investigator considers optimal, with input from the CIC, and on the basis of the subject's overall clinical and metabolic status.

Reinstitution of cornstarch therapy should be considered under the following circumstances:

- The subject has increasing frequency of documented episodes of symptomatic hypoglycemia
- The subject has increased rate or duration of prolonged hypoglycemic episodes recorded on CGM and confirmed by SMBG
- The subject experiences a time of increased metabolic demand, such as intercurrent viral infection or during treatment with steroids/placebo steroids

Every decision to reinstitute cornstarch therapy should be done after informing and discussing with the unblinded Medical Monitor and the CIC. After reinstitution of cornstarch therapy and resolution of intercurrent illness (if applicable), if the subject is clinically and metabolically stable, modifications can be considered again as detailed above in Section 7.1.2.1.

7.1.2.2.1. Modifications to Nutrition Plan After Dosing

No substantial changes should be made to nutritional intake from Baseline through the EOS Visit. It is recommended that mean weekly carbohydrate intake remains ≥ 60% of total calories from food and cornstarch, unless modified by the Investigator or study dietitian to maintain the target blood glucose range. However, < 60% of calories from carbohydrate from food and cornstarch will not be considered a protocol deviation. If nutritional modifications need to be made to carbohydrate from food to maintain the target blood glucose range, they should occur only once cornstarch has been modified as recommended by the protocol (cornstarch management guide) or advised by the Central Independent Committee. Failure to comply with this rule will constitute a protocol deviation unless the Investigator is able to provide a valid reason for bypassing protocol and CIC recommendations.

Any changes to the nutrition prescription should be documented in the source document and in the EDC. Stability will be monitored and defined as ≤ 25% variance in grams of carbohydrate from actual intake of food and beverage (not including cornstarch) compared to subject's current nutrition prescription recorded in the EDC. If the variance in grams of carbohydrate is > 25%, outside of a nutritional intervention for medical management, the subject should receive nutrition counseling from a skilled and experienced medical professional (Investigator or study dietitian) to resume an optimal diet and maintain carbohydrate stability. The nutrition counseling session should be recorded in the subjects' study chart and any changes to the subject's nutrition prescription should be documented in the source document and recorded in the EDC. Variation > 25% in grams of carbohydrate from food will not be considered a protocol deviation.

7.1.3. Number of Study Sites

Study subjects will be enrolled at approximately 23 global study sites in North America, Europe, and Brazil.

7.1.4. Number of Subjects

Approximately 50 subjects will be enrolled and randomly assigned in a 1:1 ratio to receive DTX401 (n = 25) or placebo (n = 25). Approximately 20 subjects 8 to < 18 years of age will be enrolled. Randomization will be stratified by age (< 18 years vs ≥ 18 years) and baseline percentage of values in the target blood glucose range (< 60%, ≥ 60% and ≤ 85%, > 85%).

If a subject withdraws from the study after randomization, the subject will not be replaced.

7.1.5. Rationale for Study Design

This is a randomized placebo-controlled trial, as there is no adequate comparator treatment for GSDIa patients. Approximately 50 subjects with a confirmed diagnosis of GSDIa and clinically stable disease will be enrolled and randomly assigned in a 1:1 ratio to receive DTX401 (n = 25) or placebo (n = 25). In this study, approximately 20 subjects 8 to < 18 years of age will be enrolled. Randomization will be stratified by age (< 18 years vs ≥ 18 years) and baseline percentage of values in the target blood glucose range (< 60%, ≥ 60% and ≤ 85%, > 85%).

Pediatric patients less than 8 years of age will not be eligible for entry into the clinical study. The rapid rate of liver growth that occurs from birth to the age of 8 years may limit the effectiveness of DTX401 in this age group. Nonclinical studies demonstrate that AAV8 vector administration in mice after 3 weeks of age results in stable vector genome expression, compared with administration at ≤ 2 weeks of age, which results in loss of vector expression and efficacy (Wang et al., 2011). Similarly, in nonhuman primates, loss of vector DNA in the liver was observed when dosed at ≤ 1 month of age, but no significant loss was observed when dosed at 2 to 3 years of age. The age range at which stable vector genome expression is achieved in mice and nonhuman primates corresponds to a human age range of 4.8 to 7.1 years, based on liver size. Thus, based on these nonclinical considerations, the pediatric age range of 8 to 18 years of age allows for treatment as early as is feasible to avoid substantial loss of therapeutic benefit due to rapid liver growth.

The proposed pediatric age range of 8 to < 18 years considers the safety and potential benefits of DTX401, the pathophysiology of GSDIa, and the mechanism of action of DTX401.

Subjects selected for screening should have stable disease and stable and optimized cornstarch, dietary and glycemic control and no hospitalization for severe hypoglycemic events during the 4-week period preceding screening. Enrolling subjects with stable disease management (which will be formally assessed during screening) is important for GSDIa to ensure that changes observed during the study are the result of DTX401 and not improvements in dietary management once subjects are overseen in a clinical trial setting.

Severe liver disease and markedly elevated transaminase and bilirubin levels (other than those linked to Gilbert syndrome or chronic hemolysis) or use of illicit drugs that may interfere with liver metabolism or glycemic control are exclusion criteria because gene transfer may be less efficient when inflammation is present in the liver and to exclude patients who may be at risk of liver transplant during the study. Positive results from the urine drug screen that are due to a

prescribed medication may be allowed if not impacting glycemic control and liver function and after agreement with the Sponsor. For the purposes of this protocol, the use of recreational cannabis products is not allowed, even if legal in the region where the patient lives.

Detectable pre-existing antibodies to the AAV8 capsid is an exclusion criterion and will thus exclude subjects whose immune system would preclude therapeutic benefit from DTX401.

The primary efficacy analysis will be performed after all subjects have completed the Week 48 Visit (the PEAP). The primary endpoint of percent change in daily cornstarch intake from Baseline to Week 48 (for superiority) is a clinically meaningful measure of the efficacy of DTX401.

Clinically meaningful secondary endpoints of change in total daily doses of cornstarch, change in percentage of values in the hypoglycemic range of <70 mg/dL (test for noninferiority and if that is established then test for superiority), and improvements in subject experience of the disease further support the efficacy of DTX401.

Upon completion of the PEAP, subjects who were originally assigned to placebo and have no detectable anti-AAV8 antibodies or significant change in disease status will receive blinded treatment with DTX401 following assessments at the Week 48 Visit.

The Follow-up Period (Week 48 to Week 144) will further characterize the changes in clinically meaningful glucose control after DTX401 administration and will provide extended efficacy and safety information (up to 144 weeks) to inform the overall risk-benefit profile.

For the primary endpoint, a sample size of 50 subjects (1:1 randomization ratio with 25 subjects in the DTX401 Group and 25 subjects in the Placebo Group) will provide approximately 91% power to detect a difference between the DTX401 Group and the Placebo Group at Week 48, assuming a minimum average cornstarch reduction at 50% or more in the DTX401 Group at Week 48 versus a maximum average of 10% cornstarch reduction or less in the Placebo Group at Week 48, with a common standard deviation (SD) of 40%, a correlation coefficient of 0.4 between assessments, and discontinuation rate of 10%. (Section 11.3.2.1). The primary analysis method will be a mixed model for repeated measures (MMRM) including repeated measures at Week 24, Week 30, Week 36, Week 42, and Week 48. In the Phase 1/2 clinical study 401GSDIA01, based on cornstarch data from 12 subjects at Week 52 post IP administration compared to baseline values, reduction in cornstarch intake was more than 50% in 9 subjects, 6 of whom reduced cornstarch consumption by more than 70% and 2 of whom were completely weaned from cornstarch consumption by Week 52 (Table 9).

Table 9: Percent (%) Cornstarch Reduction (Study 401GSDIA01)

Percent (%) Cornstarch Reduction at Week 52 Compared to Baseline	**20-30**	**30-40**	**40-50**	**50-60**	**60-70**	**70-80**	**80-90**	**90-100**
Number of subjects	1	1	1	2	1	3	0	3

Note: Columns for cornstarch reduction between 0 to 20% are omitted because all subjects had a > 20% reduction in cornstarch.

All primary and secondary endpoints in Phase 3 are designed in a complementary manner to report efficacy outcomes that explore multiple facets of GSDIa physiology and are tied to subjects reporting their own perceived clinical benefit, such as greater mental clarity, more energy, and weight loss.

7.1.5.1. Blinding Strategy

Study DTX401-CL301 uses a double-blind placebo-controlled design. Both IP (DTX401 or placebo) and the oral prednisolone/placebo taper will be blinded. The blind will be maintained for the subjects, Investigators and site study teams, to the extent that is safe and medically feasible, during the study until the last subject completes Week 96 visit or withdraws early. Site-facing Sponsor personnel will remain blinded until the last subject completes Week 96 visit or withdraws early. Some Sponsor personnel who are not site-facing will become unblinded to perform the PEAP analysis following database lock for the PEAP. The Dexcom CGM system will remained blinded to subjects/caregivers until the subject completes their Week 96 visit, after which it will be unblinded.

However, baseline characteristics and assessments will be unblinded in order to confirm that subjects comply with eligibility criteria and for awareness of the baseline characteristics of the study population.

Details regarding blinding strategy are provided in Table 10. Further details for clinical site staff regarding the study blind processes are available in both the Global Blinding Plan and the Site-Specific Blinding Plan. Details of blinding of Ultragenyx personnel after the database lock for the PEAP are described in the Global blinding plan.

Table 10: Blinding Strategy

	Blinded	Unblinded
Investigator	• IP (DTX401) and steroids • Crossover at Week 48 (infusions of DTX401 and saline) • Post-dose immunogenicity assessments except Week 36 AAV8 Tab results for placebo subjects who show development of antibodies to AAV8 and are ineligible to proceed beyond Week 48 • Disease-specific patient reported assessments	• Cornstarch prescription, subject cornstarch intake reported in eDiary • SMBG data • CGM data • CFC full results and central lab results • AEs
Subject/Caregiver	• IP (DTX401) and steroids • Crossover at W48 (infusions of DTX401 and saline) • CGM data (Until their Week 96 visit is completed) • Central lab results • Post-dose immunogenicity assessments except Week 36 AAV8 Tab results for placebo subjects who show development of antibodies to AAV8 and are ineligible to proceed beyond Week 48	• Cornstarch (blinding not possible due to taste) • CFC outcomes • SMBG results • AEs • CGM values from second CGM device during CFC only[a] • Disease-specific patient-reported assessment • CGM data (After their Week 96 visit is completed)
Overseeing Committee (DMC, CIC, independent Medical Monitor)	NA	Unblinded to IP, steroids and all assessments needed to fulfil their role (safety, CS and steroid management)
Sponsor, including Study Medical Lead[b]	Blinded to IP (DTX401) and steroids until primary database lock at the time of the MAA (or unblinding request from the DMC)	To fulfill their role, a small number of Sponsor staff (e.g., supply chain, pharmacy, regulatory operations, clinical systems) will be unblinded to the IP and steroids.

[a] During CFC, to maintain subject safety (if there is a sudden change in glucose levels), an additional CGM device offering real-time readings may be worn by the subject at the discretion of the Investigator.

[b] Selected Sponsor's staff (e.g., Clinical Operations, Data Management groups, clinical site monitors etc.), will have access to the data available within the clinical database as necessary for them to perform their role; they will not be unblinded to study treatment.

AE, adverse event; CFC, controlled fasting challenge; CGM, continuous glucose monitoring; CIC, central independent committee; CRA, Clinical Research Associate; CS, cornstarch; DMC, Data Monitoring Committee; IP, investigational product; MAA, marketing authorization application; NA, not applicable; SMBG, self-monitored blood glucose; W, week

All subjects receiving DTX401 (either on Day 1 or at Week 48) will receive a blinded prophylactic prednisolone regimen to minimize or prevent potential vector-induced hepatic effects (ie, transaminase elevations). Subjects receiving placebo IP infusion will receive a matching oral placebo regimen to maintain the blind. During the study, additional oral prednisolone may be administered during or after completion of the taper if a subject's alanine

aminotransferase (ALT) levels increase from baseline and/or above the upper limit of normal (ULN) of recently tested levels repeated one more time as soon as possible. In these cases, the Investigator will remain blinded, and the CIC will recommend the appropriate treatment regimen until transaminase elevation is resolved. In order to maintain the blind for Investigators and sites, additional sham steroids (ie, the matching placebo) will be administered randomly in subjects who received placebo IP, and when deemed appropriate to match the same conditions as with DTX 401-treated subjects. Additional tests may need to be conducted in both groups based on the assessment of the CIC (ie, cases in which ALT elevations occur in placebo or DTX401 subjects).

On the day of infusion, a blinded infusion bag will be prepared by an unblinded pharmacist who will have no direct interaction with subjects and will be required to not unblind the study staff and the Principal Investigator (PI). Once prepared, the DTX401 infusion is clear and colorless. The proposed matching placebo is a saline IV infusion in a matching infusion bag. Infusion bags will be centrally supplied in order to ensure similar marking and labels. Preparation times for DTX401 and placebo should be equivalent. Infusion instructions will be the same for both treatment groups. Drug accountability for the preparation of the infusion will be performed by an unblinded pharmacy monitor that has no blinded subject data monitoring obligations.

Laboratory results for the Week 36 AAV8 TAb assay could potentially unblind anyone viewing these results. Therefore, the Investigators will not receive these results until the end of the study, and only the independent Medical Monitor will have access to these data. Prior to IP administration at Week 48, the unblinded Clinical Trial Manager (overseeing the pharmacy monitor) will review results from the Week 36 AAV8 TAb assay for eligibility for IP administration at Week 48. The Investigator will review the Week 36 assessments as soon as they are available and the Study Continuation Criteria (Section 8.3) to confirm that the subject is eligible to receive IP administration at Week 48. If there is evidence of any change from baseline in disease status or overall well-being that would preclude safe administration of DTX401, the Investigator will consult the Medical Monitor. If a prolonged Holding Period is required, Study Continuation Criteria will be reviewed prior to the second IP administration to confirm the subject is able to receive IP administration at Week 48. The AAV8 TAb assay should be repeated prior to IP administration if more than 6 months have elapsed since the last measurement (i.e., in the unlikely event that a subject remains in a holding pattern for more than 6 months).

As another measure to maintain the blind, disease-specific patient-reported assessments (eg, the Glycogen Storage Disease Functional Assessment Diary [GSD FAD], Patient Global Impression of Severity [PGIS], and Patient Global Impression of Change [PGIC]) will be completed individually on an electronic device throughout the study, further reducing exposure to study personnel. Subjects will be instructed not to discuss the study on social media or in other public forums where other study subjects may become aware of individual results.

Subjects will be blinded to their CGM data until the subject reaches the Week 96 visit, which will not synchronize with their usual reading devices and for which alarms will be deactivated in their device. Weekly reports will be automatically generated with actual CGM data and will be shared with the Investigator at the beginning of the following week. The Investigator will not reveal the results to the study subject but will request capillary glucose verification for any clinically significant out-of-range values.

SMBG and CGM results will also be provided to the CIC to facilitate communication with the Investigator and verify that the cornstarch management guide is applied promptly and appropriately (Section 7.1.2). The CIC will review SMBG, CGM, cornstarch and dietary intake data when needed (prompted by the unblinded Medical Monitor) throughout the study to provide guidance on cornstarch management to Investigators.

Self-measured capillary blood glucose measurements (ie, SMBG), cornstarch prescription, and dietary instructions will not be blinded during the study to the subject or the Investigator, as these form the basis of subject management and follow individual subject needs. It would not be safe or medically feasible to create a placebo cornstarch to maintain a constant weight for consumption.

7.1.6. Dose Rationale

A dose of 6.0×10^{12} GC/kg was selected as the optimal biologic dose (OBD) for DTX401, based on the Phase 1/2 clinical study (Study 401GSDIA01). Efficacy and safety data reviewed through Cohort 3 Week 12 revealed that the 6.0×10^{12} GC/kg dose was associated with faster reductions in cornstarch intake compared with the lower dose (2.0×10^{12} GC/kg) and there were no significant safety findings. As part of ongoing improvements to manufacturing and quality control, the method for determining vector genome titer (GC/mL) has been updated with an improved more precise assay. A conversion factor has been established that changes the label concentration for Phase 3. As such, the OBD numerical value is updated to 1.0×10^{13} GC/kg (per Droplet Digital™ polymerase chain reaction [ddPCR]) for Phase 3. This OBD is equivalent to the 6.0×10^{12} GC/kg OBD (per qPCR) that was determined in the Phase1/2 trial and measured by the initial (more variable) Phase 1/2 vector genome titer assay.

7.2. Duration

7.2.1. Duration of Subject Participation

The planned study duration is approximately 162 weeks (with possible extension if a subject enters a holding period), including the following:

- Predosing period of up to 18 weeks: Subjects may be randomized as soon as nutrition optimization and 4 consecutive weeks of diet, cornstarch, and blood glucose control stability are demonstrated. Subjects will have up to 16 weeks to achieve nutritional optimization and stability prior to randomization and up to 10 days (approximately 2 weeks) from randomization to dosing. See details in Section 7.1.1.
- PEAP: 48 weeks
- Follow-up Period of 96 weeks

Upon completion of this study (EOS or Early Withdrawal), all subjects who receive DTX401 will be asked to enroll in a long-term follow-up study to evaluate safety and effectiveness of DTX401 via the DMP for at least 10 years after DTX401 administration. The DMP for GSDIa will be conducted under a separate protocol.

7.2.2. Primary Analyses and End of Study Definition

Primary analyses for all primary, secondary, and tertiary endpoints will be performed after all subjects have completed the Week 48 Visit. All data, including data obtained after the Week 48 Visit at the time of primary database lock, will be included in the analyses. These analyses will be repeated at Week 96 and at the end of the study (Week 144). The end of the study is defined as the date of the Week 144 Visit (or Early Withdrawal Visit, if applicable) for the last participant enrolled in the study.

7.3. 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 Institutional Review Board (IRB)/Ethics Committee (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 the IRB/EC to prioritize reporting of protocol deviations that impact the safety of trial participants.

8. POPULATION

Prospective protocol deviations for recruitment and eligibility criteria (ie, protocol waivers or exemptions) are not permitted.

8.1. Inclusion Criteria

Eligible individuals must meet all of the following criteria, unless otherwise noted, during Screening and Randomization Period:

1. Male and female patients ≥ 8 years of age at time of informed consent or assent.
2. Subject has a diagnosis of GSDIa confirmed by deficient enzymatic activity (on liver biopsy), or by molecular testing of *G6PC* gene revealing 2 pathogenic mutations. In the case where only a single pathogenic mutation is identified, clinical diagnosis is compatible with GSDIa and absence of characteristic features of GSDIb (ie, chronic neutropenia, inflammatory bowel disease).
3. Subject is currently receiving a therapeutic regimen of cornstarch (or equivalent), following international guidance/recommendations (see Appendix 1) with stable nutrition, glycemic, and clinical status, as evidenced by:
    a. No more than a 10% variation in weekly average daily cornstarch (or equivalent) intake over the last 4 weeks.
    b. No more than a 25% variation in weekly average daily non-cornstarch carbohydrate over the last 4 weeks.
    c. No more than 15% variation in weekly percentage of values in the target blood glucose range (60-120 mg/dL) over the last 4 weeks as measured by CGM and corroborated by SMBG. If adequate corroboration is not observed, this assessment should be made by SMBG.
    d. No hospitalization for hypoglycemia and no severe hypoglycemic event (SHE) during the 4-week period preceding randomization and dosing (see Section 10.4.2 for more detail on SHE), notwithstanding events of hypoglycemia due to unavoidable and unforeseeable events (e.g., infection, trauma) that transiently prevent the subject from tolerating enteral intake or acutely change the subject's metabolic demands, provided that the subject quickly returns to their prior physiologic state.
4. Subject is willing and able to comply with study procedures, requirements, and study medication, including periodic inpatient hospitalization or admission in a research facility; CFC studies; frequent blood collection; wearing a CGM device for the duration of the study (and excluding the use of any non-study CGM or flash glucose device); performing capillary glucose measurements according to the protocol using a study-approved glucometer (and excluding the use of any other glucometer); completing an eDiary to track daily cornstarch, diet intake, and reasons for doing SMBG routinely throughout the study as required by the protocol; and completing patient-reported questionnaires. Subject must strictly comply with the prednisolone/placebo prednisolone prescription including changes in prescription that may be implemented during the study by the Investigator, if needed. See Section 9.2, Prednisolone Taper. If < 18 years (or as required by region), has a parent or legal guardian willing and able to assist with study requirements.

5. From the period following informed consent through the duration of participation in the study, female subjects of childbearing potential and fertile male subjects must consent to use highly effective contraception as defined by the Food and Drug Administration (FDA) and Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (Version 1.1 dated 21 Sep 2020). Female subjects must agree not to become pregnant and male subjects must agree not father a child or donate sperm for at least 48 weeks after the last dose of IP if they decide to withdraw early from the study.
6. Subject is willing and able to provide written informed consent after the study has been explained and before any study-related procedures are performed. If < 18 years (or as required by region), willing and able to provide written assent and have a parent or legal guardian willing and able to provide written informed consent after the study has been explained and before any study-related procedures are performed.

8.2. Exclusion Criteria

Eligible individuals must not meet any of the following criteria, unless otherwise noted, during the Screening and Randomization Period:

1. Detectable pre-existing antibodies to the AAV8 capsid during Screening.
2. History of liver transplant, including hepatocyte cell therapy/transplant.
3. History of severe hepatic fibrosis or cirrhosis as evidenced by any of the following: portal hypertension, ascites, splenomegaly, esophageal varices, hepatic encephalopathy, or a liver biopsy with evidence of stage III fibrosis.
4. Presence of liver adenoma > 5 cm in size or presence of liver adenoma > 3 cm and ≤ 5 cm in size with a documented annual growth rate of ≥ 0.5 cm per year.
5. Significant hepatic injury or dysfunction as evidenced by imaging or any of the following laboratory abnormalities from 2 consecutive samples (collected at least 4 weeks apart). Liver function tests may be repeated during Screening at the Investigator's discretion; those with initially abnormal values may be retested and the subject will qualify for this criterion if the most recent results during Screening are within the allowed range:
   - ALT or aspartate aminotransferase > 2.5 × the upper limit of normal (ULN)
   - Total bilirubin > ULN unless the subject has Gilbert syndrome
   - Alkaline phosphatase > ULN, with gamma-glutamyl transferase > ULN
6. Presence or history of hepatitis B virus infection, hepatitis C virus infection, or both.
7. Non-fasting triglycerides ≥ 1000 mg/dL. For the purposes of this study, non-fasting refers to the longest fasting period that each individual subject is able to tolerate. Depending on the meal and cornstarch schedule, the blood draw could occur in the morning before breakfast or before the first dose of cornstarch. Triglycerides may be repeated during the Screening Period at the Investigator's discretion and those with abnormal values may be retested. The study subject will qualify for this criterion if the most recent results during Screening are within the allowed range.

8. Human immunodeficiency virus infection AND any of the following: CD4+ cell count < 350 cells/mm^3, change in antiretroviral therapy regimen within 6 months before baseline, or plasma viral load > 200 copies/mL on 2 separate occasions as measured by polymerase chain reaction.
9. Presence or history of any disease or condition that, in the Investigator's opinion, would interfere with the subject's safety or ability to participate in the study or would significantly affect interpretation of study results. This includes any intercurrent febrile or nonfebrile illness including common viral infections, epidemic influenza and other viral illnesses, and coronavirus disease 2019 (COVID-19) until full clinical recovery.
10. Female subjects of childbearing potential who have a positive pregnancy test, who are unwilling to use contraception, or are unwilling to have additional pregnancy tests during the study.
11. Pregnant, breastfeeding, or planning to become pregnant (self or partner) at any time during the study.
12. Presence or history of any hypersensitivity to the excipients of DTX401 or placebo or to prednisolone, or inability to swallow capsules that, in the judgment of the Investigator, places the subject at increased risk for adverse effects.
13. Current or previous participation in another gene transfer study.
14. Use of any IP or investigational medical device within 3 months preceding screening or planning to use at any time during the study.
15. History of illicit drug use within 60 days prior to screening or positive results from a 9-panel urine drug screen prior to dosing and completed at 2 time points at least 4 weeks apart. Positive results that are due to a prescribed medication may be allowed if not impacting glycemic control and liver function and after agreement with the Sponsor. For the purposes of this protocol, the use of recreational cannabis products is not allowed, even if legal in the region where the patient lives.

8.3. Study Continuation Criteria

All subjects will be evaluated according to Study Continuation Criteria prior to their second IP administration at Week 48. Subjects who meet any of the following exclusion criteria may not receive blinded IP at Week 48 but will complete all other Week 48 assessments. The decision to continue with study assessments beyond Week 48 will be determined by the Investigator and Sponsor Medical Monitor, based on the following:

1. Positive antibodies to AAV8 capsid, collected at Week 36 (or during the Holding Period if required) if the subject was allocated to placebo at Baseline.
2. Liver tests that meet DILI thresholds for serious liver injury (Table 11) at Week 48, or any clinically significant changes from baseline in liver tests that in the judgment of the PI or unblinded Medical Monitor would interfere with safety of blinded IP infusion at Week 48 or would significantly affect interpretation of safety and efficacy results.

3. Presence of any abnormality, in the Investigator's opinion, that would interfere with the subject's safety or ability to continue participating in the study or would significantly affect interpretation of study results.
4. Female subjects of childbearing potential and fertile male subjects unwilling to continue to use highly effective contraception as defined by the Food and Drug Administration (FDA) and Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (Version 1.1 dated 21 Sep 2020).
5. Female subjects unwilling to continue pregnancy testing or who plan to become pregnant or breastfeed within 48 weeks after the last dose of IP.
6. Male subjects unwilling to agree not to father a child or donate sperm for at least 48 weeks after the last dose of IP.

Due to the nutrition adjustments throughout the treatment period, nutrition, glycemic and expected metabolic stability do not form part of the Study Continuation Criteria. However, the Investigator should discuss any concerns about nutritional, glycemic or metabolic stability (e.g., severe hypoglycemia, significantly elevated triglycerides, etc.) with the unblinded Medical Monitor before proceeding with the second IP administration at Week 48.

8.4. Subject Discontinuation and Stopping Rule Criteria

8.4.1. Subject Withdrawal

Subjects have the right to withdraw from the study at any time for any reason. Ultragenyx must be notified of all subject withdrawals as soon as possible. Ultragenyx also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an Investigator due to poor enrollment or noncompliance, as applicable.

Notwithstanding study termination, all subjects who receive DTX401 will be followed for the collection of long-term safety information. If a subject considers withdrawing from the study early, reasonable efforts will be made to continue collecting safety information for the subject through the End of Study (Week 144) Visit. After completion of the End of Study Visit, long-term follow-up will occur in a long-term follow-up study (DMP) for GSDIa subjects who received DTX401.

If a subject withdraws from the study early, reasonable efforts will be made to complete Early Withdrawal Visit assessments as soon as possible, and the subject will be encouraged to enroll in the DMP for GSDIa for long-term follow-up. If a subject withdraws consent to participate in the study, the site may continue to contact the subject's health care provider (HCP) or review available public information to determine the subject's survival status as described in Section 10.4.11.

If a subject withdraws from the study after randomization, the subject will not be replaced. If a subject withdraws from the study after signing the ICF but before randomization, the subject will be replaced.

8.4.2. Study Discontinuation, Pausing, or Suspending Enrollment

Study enrollment and any pending IP administration will be paused, and the DMC and regulators will be notified if, at any time during the study, any of the events listed below occur after DTX401 administration:

- Death of a subject
- 2 subjects experience a serious liver injury as defined by drug-induced liver injury (DILI) thresholds in Table 11, deemed related to DTX401 by the DMC or Ultragenyx. If a subject meets any of the thresholds in Table 11, the subject will be closely monitored until the biochemical abnormalities and clinical symptoms, if present, normalize or stabilize.

Table 11: DILI Threshold Definitions for Serious Liver Injury

For subjects with ALT and AST < ULN at Baseline	**For subjects with ALT or AST ≥ ULN at Baseline**
ALT or AST ≥ 3 × ULN and TB ≥ 2 × ULN	ALT or AST ≥ 3 × baseline level and TB ≥ 2 × ULN
ALP ≥ 2 × ULN and TB ≥ 2 × ULN	ALP ≥ 2 × ULN and TB ≥ 2 × ULN
ALP ≥ 2 × ULN and DB ≥ 2 × ULN (for patients with Gilbert's syndrome)	ALP ≥ 2 × ULN and DB ≥ 2 × ULN (for patients with Gilbert's syndrome)
ALT or AST ≥ 3 × ULN and INR ≥ 1.5	ALT or AST ≥ 3 × baseline level and INR ≥ 1.5
ALP ≥ 2 × ULN and DB or TB ≥ 2 × ULN and INR ≥ 1.5	ALP ≥ 2 × ULN and DB or TB ≥ 2 × ULN and INR ≥ 1.5
ALT or AST ≥ 8 × ULN	ALT or AST ≥ 8 × ULN
Hepatic decompensation (ie, hepatic cirrhosis or acute liver failure)	Hepatic decompensation (ie, hepatic cirrhosis or acute liver failure)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, direct bilirubin; DILI, drug-induced liver injury; INR, international normalized ratio; TB, total bilirubin; ULN, upper limit of normal

- An SAE with a severity of ≥ Grade 3, according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (DHHS, 2017), unless upon Sponsor assessment are clearly unrelated to IP or protocol procedures and are:
  - biologically implausible (eg, animal bite)

    or
  - a known complication of the disease occurring at the expected frequency in GSDIa assessed as not related to worsening of disease

If any of the above events occur, study enrollment and any pending IP administration will be paused, and the Sponsor and DMC will conduct a causality assessment. The study continuation will be discussed with the FDA and other applicable regulatory authorities.

An event that meets the above criteria will be reported immediately to the Sponsor once the study site becomes aware (within 24 hours). Serious AEs will be reported as outlined in Table 20. For AEs and SAEs, the appropriate pages of the CRF must be completed. 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.

If study enrollment and Week 48 IP administration are suspended, all currently enrolled subjects will remain in the study and will continue to be monitored through their completion (ie, EOS) or withdrawal from the study.

8.5. Informed Consent

Informed consent must be obtained from the subject or obtained by a legally authorized representative with the subject's assent in the case of a minor and according to country regulations, before performing any study-related procedures. If a minor reaches legal age during study participation, informed consent must be obtained from that subject for continued participation in the study. If a subject is rescreened for the study, a new ICF must be signed.

8.6. Screening Requirements

All screening evaluations specified in Table 3 must be completed and reviewed to confirm eligibility. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Subjects who do not meet eligibility requirements (for assessments that are allowed to be repeated, eg, glycemic, diet, and cornstarch stability, triglycerides and liver function tests) within the Screening Period may be rescreened once during the study. In this case, only AAV8 antibody testing 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. If a subject is rescreened for the study, a new ICF must be signed.

Screening assessments may be completed in any reasonable order (except where indicated) and on more than one day at the Investigator's discretion. It is recommended that samples for the AAV8 TAb assay and *G6PC* genotyping be collected as soon as possible after the subject/guardian signs the ICF, preferably on the same day, and the liver ultrasound should also be scheduled as soon as possible. The subject/caregiver should be given the CGM system, blood glucose monitor, and the eDiary to start collecting baseline data immediately after the signing the ICF (unless deemed ineligible by that time). If a subject is no longer eligible for study participation, all devices should be returned.

At the Screening Visit, informed consent will be obtained, and general medical information (ie, demographics, relevant medical and GSDIa history) will be collected as allowed by local laws and regulations. Medical condition or event, start date, end date, and status will be recorded on the appropriate page of the CRF. 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 CRF.

Prior to dosing in Year 1 of the study, a 9-panel urine drug screen will be completed at 2 time points at least 4 weeks apart (Table 3). Subjects who have a positive test will not be enrolled into the study. Positive results that are due to a prescribed medication may be allowed if not

impacting glycemic control and liver function and after agreement with the Sponsor. For the purposes of this protocol, the use of recreational cannabis products is not allowed, even if legal in the region where the patient lives.

9. INTERVENTIONS

An overview of all interventions, including IP, placebo, prednisolone and premedication is provided in Table 12.

Table 12: Study Interventions

Intervention	DTX401	Placebo for DTX401 (Normal Saline)	Prednisolone	Placebo for Prednisolone	Acetaminophen/ Paracetamol	2nd generation H1 antagonist (cetirizine or equivalent)	H2 antagonist (famotidine or equivalent)
Dose formulation	2.8×10^{13} GC/mL[a]	0.9 % sodium chloride	5 mg or 10 mg gelatin capsules	Tablets matching prednisolone	Tablet	Tablet	Tablet
Unit dose strength/ dosage level	1×10^{13} GC/kg, single infusion	n/a	Weight-based dose taper (Section 9.2)	n/a	12.5 mg/kg, up to max dose of 1 g	10 mg for cetirizine	0.5 mg/kg, up to max dose of 40 mg for famotidine
Route of administration	IV infusion	IV infusion	Oral	Oral	Oral	Oral	Oral
Use	Experimental agent	Placebo comparator to DTX401	Prophylaxis: prevention of vector-induced hepatic effects	Placebo to maintain study blind	Premedication[b]	Premedication[b]	Premedication[b]

[a] Target concentration measured using a ddPCR method; release acceptance criteria: $\geq 7.3 \times 10^{12}$ to $\leq 9.0 \times 10^{13}$ GC/mL

[b] The study site will supply premedication that will be obtained locally

ddPCR, Droplet Digital polymerase chain reaction; GC, genome copies; IV, intravenous

9.1. Investigational Product

9.1.1. 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.

Investigational product is manufactured, packaged, and labeled according to current Good Manufacturing Practices. 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.

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.

Additional information on physical and chemical properties of DTX401 are provided in the IB. Investigational product accountability requirements are summarized in Appendix 6.

9.1.2. Reference Therapy

Patients randomly assigned to placebo will receive a single peripheral IV infusion of normal saline. Infusion bags will be centrally supplied to ensure similar marking and labels.

9.1.3. Preparation and Administration

The study site will be provided with the supplies required for infusion of IP (DTX401 or placebo).

DTX401 will be administered as peripheral IV infusion at a dose level of 1.0×10^{13} GC/kg (as determined based on product vector titer [GC/mL] measured by ddPCR). Note that with the application of the Phase 1/2 to Phase 3 conversion, the quantity of IP administered as the Phase 3 OBD is identical to the OBD administered during the Phase 1/2 trial. An explanation of the conversion factor, along with the rationale for the assay change is described in "White Paper on Use of ddPCR instead of qPCR for Establishing Target Concentration, Lot Release and Patient Dosing."

The dose of DTX401 to be administered will be calculated using the subject's weight recorded at screening (for Day 1 IP administration) or at Week 36 (for Week 48 IP administration). Any subject weighing > 90 kg will be dosed as if his or her weight is 90 kg.

Prior to receiving IP, the subject should achieve 4 consecutive weeks of clinical stability (as described in Section 7.1.1). The Screening Period may be extended by the Sponsor up to 112 days, to achieve this aim before administration of IP. The subject's weight will be verified 1 day before administration of DTX401 to ensure that their current weight is within 10% of their

screening weight for Day 1 dosing and within 10% of their Week 36 weight for Day 338 Dosing. Subjects with a confirmed change in weight that is > 10% from screening for Day 1 dosing or > 10% weight change from Week 36 for Day 338 dosing 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 should be dosed as follows:

- If a subject's weight has increased, their weight at Screening or Week 36 should be used to determine the Day 1 or Day 338 dose, respectively
- If a subject's weight has decreased, dose adjustments may be made if deemed necessary

Changes in subject weight and potential impact to dosing will be discussed with the Sponsor as needed.

Because beta-blockers can antagonize the response to epinephrine, subjects taking beta-blockers should temporarily stop the medication 24 to 72 hours prior to IP administration. If holding beta-blockers is not feasible, glucagon should be available for reversal of beta-blocker effects during anaphylaxis.

On the day of infusion, a blinded infusion bag will be prepared by an unblinded pharmacist who will have no direct interaction with subjects. A saline IV infusion in a matching standard infusion bag will be prepared by the unblinded pharmacist for subjects randomly assigned to placebo. Drug accountability for the preparation of the infusion will be performed by an unblinded pharmacy monitor who has no blinded subject data monitoring obligations.

Subjects will be premedicated 30 to 60 minutes prior to the start of blinded IP infusion, with acetaminophen/paracetamol, 2nd generation H1 antagonist (eg, cetirizine, loratadine, fexofenadine) and a H2 antagonist (eg, famotidine). Refer to Table 12 for additional details.

The blinded IP will be administered by qualified study personnel, as designated by the Investigator. Infusion instructions will be the same for both treatment groups.

Detailed instructions for dose preparation and subsequent infusion of DTX401 are provided in the Pharmacy Manual.

The start time, stop time, and volume of infusion will be recorded.

9.1.4. Clinical Observation and Supportive Care

An appropriately trained medical professional must be at the bedside to observe the subject for the first 5 minutes after the start of the IP infusion. Vital signs will be measured at the following time points:

- Immediately prior to the start of the infusion
- Approximately 5, 10, 15, 30, 45, 60, 75, 90, 105 minutes after the start of the IP infusion
- Approximately 2, 2.5, 3, 3.5, 4, 4.5 5, 5.5, 6 hours (± 5 minutes) after the start of the IP infusion.
- A pulse oximeter will be continuously used for the full duration of the infusion to monitor O_2 saturation.

- If the infusion is interrupted due to an infusion-related reaction, timing of vital sign measurements should match the above sequence when the infusion is restarted. An appropriately trained study staff member should be at the bedside for the remainder of the infusion.
- Monitoring of vital signs will continue for at least 6 hours after the completion of the infusion in a site that is appropriately equipped to treat anaphylaxis, and the subject should be monitored until all infusion-reaction symptoms have resolved.

On the days of IP administration, a blood sample for analysis of clinical chemistry (including liver function tests [LFTs]) will be collected approximately 0.5 and 2 hours after the start of the IP infusion and sent to the local laboratory. Additional blood samples for clinical chemistry may be collected during the post-IP infusion observation period if clinically indicated.
The Investigator should review the laboratory results before the subject is discharged.

Premedication with acetaminophen/paracetamol, 2nd generation H1 antagonist (eg, cetirizine, loratadine, fexofenadine) and a H2 antagonist (eg, famotidine) is required prior to blinded IP administration. NSAIDs should be avoided as premedication.

Patients should be closely monitored for potential infusion reactions during IP administration. If any signs or symptoms of an infusion-related reaction (IRR) are observed following administration of blinded IP, the infusion should be paused immediately. The subject should be monitored closely, and supportive care should be provided as needed (Table 13).

Examples of mild reactions include isolated mild tachycardia, rash, itching, flushing, nausea, abdominal pain, or headache. If a subject has an IRR that is mild (Grade 1) or moderate (Grade 2) in severity, and if symptoms have resolved with treatment, the infusion may be restarted at half of the prior rate if the subject, the Investigator and Medical Monitor agree to resume the infusion. Subjects should be monitored for at least 24 hours after the completion of the infusion if their initial symptoms were in any way suggestive of an allergic reaction (eg, urticarial rash, angioedema, hypotension, cough).

If IRR symptoms of mild (Grade 1) severity recur after restarting and increasing the infusion rate, the rate of infusion should be decreased to the rate prior to recurrence of the Grade 1 IRR. If symptoms resolve, the rate may be slowly increased again but should be maintained at rates lower than the rate at which the Grade 1 IRR recurred. Completion of the infusion is required within the recommended stability timeframe (7 hours) following IP reconstitution. If IRR symptoms of moderate (Grade 2) severity occur after restarting the infusion, the infusion will be stopped and will not be restarted. Subjects should be monitored for at least 24 hours after the completion of the infusion.

If a subject develops signs of any ≥ Grade 3 infusion-related reaction, the infusion should be stopped immediately, and the subject will not be re-dosed. Examples of severe reactions include severe bronchospasm, severe hypotension, anaphylaxis, or seizure.

For guidance on diagnostic criteria for anaphylaxis, see “Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis” (Shaker et al., 2020), and “Severity grading system for acute allergic reactions: A multidisciplinary Delphi study” (Dribin et al., 2021). Subject management, supportive care and symptomatic treatment should be in line with these

practice guidelines. Clinical features of allergic and nonallergic anaphylaxis can overlap, and anaphylaxis of any mechanism should be treated with epinephrine and subject will be monitored for 24 hours.

In addition to supportive care, serum tryptase, C3, C4, SC5b-9, CH50, AH50 and MBL should be measured 30 to 120 minutes after the start of an infusion-related reaction. The timing of sample collection should be documented. A second blood sample for tryptase, C3, C4, SC5b-9, CH50, AH50 and MBL measurement should be obtained at least 24 hours after symptoms have resolved. If there are challenges in obtaining blood samples, the order of sampling priority is 1) tryptase, C3, C4, and CH50, 2) AH50 and MBL, and 3) SC5b-9.

If a subject has a mild or moderate hypersensitivity reaction that is treated with antihistamines or steroids and the subject is discharged within 24 hours, the subject should be provided with an epinephrine autoinjector and instructed on its proper use.

Prior to discharge, all subjects receiving blinded IP should be provided with standard patient education materials on signs and symptoms of anaphylaxis, including guidance on when to seek emergency care.

Table 13: Infusion Instructions for Adverse Reactions

CTCAE IRR Severity	Action
Grade 1 (mild) or Grade 2 (moderate)	The infusion should be paused immediately, and the subject should be monitored closely. The Sponsor's responsible physician should be notified immediately. Supportive care, which may include IV fluids or corticosteroids, should be provided. If symptoms resolve, the infusion may be restarted at half of the prior rate with a physician at the bedside for each rate increase, if the PI, medical monitor and Sponsor's responsible physician agree and completion of the infusion is within the recommended stability timeframe (7 hours) following IP reconstitution Subjects should be monitored for at least 24 hours after the completion of the infusion if their initial symptoms were in any way suggestive of an allergic reaction (eg, urticarial rash, angioedema, hypotension, cough). If IRR symptoms of mild (Grade 1) severity recur after restarting and increasing the infusion rate, decrease the rate to the rate prior to recurrence of the Grade 1 IRR. If symptoms resolve, the rate may be slowly increased again but should be maintained at rates lower than the rate at which the Grade 1 IRR recurred. Completion of the infusion is required within the recommended stability timeframe (7 hours) following IP reconstitution. If IRR symptoms of moderate severity (Grade 2) occur after restarting the infusion, stop the infusion and do not restart it. Subjects should be monitored for at least 24 hours after the completion of the infusion.
≥ Grade 3 (severe or life-threatening)	The infusion should immediately be terminated. The subject should be closely monitored, and supportive care and symptomatic treatment should be provided. The Sponsor's responsible physician should be notified immediately. No additional blinded IP will be administered to the subject for the remainder of the study. Subjects with severe events of hypersensitivity or anaphylaxis will be observed for at least 24 hours.

CTCAE; Common Terminology Criteria for Adverse Events, Version 5.0 (HHS 2017)

9.2. Prednisolone Taper

All subjects receiving DTX401 will complete a prophylactic oral prednisolone taper regimen to minimize or prevent potential vector-induced hepatic effects (eg, transaminase elevations). Subjects receiving placebo IP infusion will receive a matching oral placebo regimen to maintain the blind. Blinded oral prednisolone and matching oral placebo taper kits will be provided by the Sponsor.

Oral prednisolone (or placebo) will be initiated 14 days after IP administration (Day 15 and Day 352), sustained for 4 weeks, and then tapered over approximately 4 weeks. As shown in Table 14, subjects weighing at least 60 kg will receive a standard dose taper while subjects weighing less than 60 kg will receive a weight-based dose taper. Doses will be based on the subject's weight at screening (for Day 1 IP administration) or at Week 36 (for Week 48 IP

administration). For subjects weighing less than 60 kg, the doses will be rounded down to the nearest 5 mg. Further details, including specific doses by weight bracket, are provided in the Pharmacy Manual.

Table 14: Prophylactic Oral Prednisolone/Placebo Taper Regimen

Duration of Dose	Prednisolone/Placebo Dose		Monitoring Phone Calls
	Subjects Weighing ≥ 60 kg	Subjects Weighing < 60 kg[a]	
4 weeks	60 mg/day[b]	1.0 mg/kg/day[b]	Investigators will call subjects to monitor for symptoms or signs of iatrogenic Cushing's syndrome and adrenal insufficiency at the end of each taper stage
5 days	40 mg/day	0.7 mg/kg/day	
5 days	30 mg/day	0.5 mg/kg/day	
5 days	20 mg/day	0.3 mg/kg/day	
5 days	10 mg/day	0.2 mg/kg/day	
10 days	5 mg/day	0.1 mg/kg/day[c]	

[a] Doses for subjects weighing < 60 kg should be rounded down to the nearest 5 mg. See pharmacy manual for details.

[b] Prednisolone/Placebo dose for subjects experiencing increased lactate or intolerable steroid toxicity after the initial 2 weeks of treatment will be reduced to 50 mg/day or 0.8 mg/kg/day (as applicable). If the intolerable effects do not begin to improve within 5 days of the dose adjustment, the subject may begin tapering (to 40 mg/day or 0.7 mg/kg/day, as applicable).

[c] For the last 10 days of dosing for subjects weighing < 25 kg, the dose should be 5 mg every other day instead of rounding the dose down to 0.

Investigators should avoid a rapid taper of prednisolone/placebo outside of the recommended regimen. Any changes from the recommended prednisolone/placebo regimen should be discussed with the unblinded medical monitor. Investigators will call subjects during the steroid tapering regimen to monitor for symptoms or signs of iatrogenic Cushing's syndrome and adrenal insufficiency. Suspicion of adrenal insufficiency should warrant endocrinology consultation and stress steroids. An early morning cortisol and ACTH should be obtained 24 hours after completing the prednisolone/placebo taper, and any abnormal levels should be reviewed by the CIC. During the study, additional oral prednisolone/placebo may be administered during or after completion of the taper if a subject's ALT levels increase from baseline and above the ULN, after verification by repeat testing, and after discussion with the unblinded medical monitor and CIC. If the rise in ALT occurs during the taper, investigators may prescribe additional steroids/placebo up to a total daily dose of 60 mg/day (or 1 mg/kg/day for subjects weighing less than 60 kg) until ALT levels return to baseline levels or return to within the normal range. The subject may thereafter restart the taper. The Investigator will remain blinded to the subject's treatment status and will determine the appropriate treatment regimen in collaboration with the unblinded medical monitor and CIC until transaminase elevation is resolved.

Standard chemistry and lactate (see Table 19) will be collected 2 weeks and 4 weeks after starting prednisolone/placebo (Week 4, Week 6, Week 12, Week 52, Week 54 and Week 60). ***Note:*** *lactate may be collected locally or by home health care vendor*. In addition to the recommended collection times, lactate may be collected at any time per Investigator judgment and discretion.

Investigators will closely monitor subjects and will consider using stress dose steroids during acute illness, trauma or surgical procedures for subjects who have completed steroid treatment within the past 12 months, especially those who have low morning cortisol. HPA axis recovery testing and/or stress dose steroids will be considered if suppression of the HPA axis is suspected. IM or IV preparations of stress-dose corticosteroids should be considered where a subject is vomiting with likely poor gastrointestinal absorption.

9.2.1. Vaccination and Oral Prednisolone Regimen

Certain vaccines, such as measles, mumps, and rubella (MMR) and varicella, which are live vaccines, are contraindicated for subjects on a substantially immunosuppressive steroid dose for more than 14 days (ie, ≥ 2 weeks of daily receipt of 20 mg of prednisolone or equivalent or 1 mg/kg/day in children under 20 kg).

Investigators should time the administration of any vaccines to be at least 1 month before administering blinded IP, or to be after completion of the 8-week prophylactic oral prednisolone/placebo regimen, considering that the highest dose is 60 mg/day or 1 mg/kg/day, depending on weight, for 4 weeks, followed by a 4-week taper regimen.

9.3. Prior and Concomitant Therapy

Subjects may receive concomitant medications as required, with the exception of those identified in Section 9.4 as prohibited. Medications (investigational, prescription, over-the-counter, and herbal), vaccinations, and nutritional supplements taken during the 30 days prior to screening will be reviewed and recorded at the Screening Visit. At the Baseline Visit, current medications will be recorded. At each visit, any concomitant medications added or discontinued during the study (including all vaccinations and nutritional supplements) should be recorded on the CRF. 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. The site personnel should record the following in the CRF: date the medication was taken, the name of the medication, medication dosage, formulation, route of administration and the reason the medication was taken.

9.4. Restricted or Prohibited Medications, Devices, and Procedures

Subjects may not be enrolled if they have used any investigational product or investigational medical device within 3 months prior to screening.

Use of another investigational product (other than DTX401) or investigational device is prohibited from screening through Week 144.

Subjects taking beta-blocker medication should temporarily stop the medication 24-72 hours prior to IP administration. If temporarily stopping beta-blockers is not possible, this should be discussed with the Medical Monitor.

History of illicit drug use within 60 days prior to screening or a positive result from a urine drug screen during the Screening Period preclude subject participation in the study. Positive results that are due to a prescribed medication may be allowed if not impacting glycemic control and liver function and after agreement with the Sponsor. For the purposes of this protocol, the use of recreational cannabis products is not allowed, even if legal in the region where the patient lives.

Subjects should abstain from consuming alcohol throughout the study.

Section 9.2 provides guidance on the timing of routine vaccinations relative to the prednisolone taper.

9.5. Treatment Assignment and Blinding

9.5.1. Treatment Assignment

This is a double-blind placebo-controlled study. Subjects who meet the eligibility criteria for randomization will be randomly assigned to a double-blind treatment group using the IRT system. The IRT will be used to assign double-blind investigational product and double-blind steroids to each subject. Subjects will be stratified by age and baseline percentage of values in the target blood glucose range at the time of randomization. Instructions for use of the IRT will be provided in the Pharmacy Manual.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each study site (numbered uniquely within a protocol), the subject number is assigned to subjects sequentially according to the order in which subjects present for screening.

9.5.1. Blinding

Study subjects, Investigators, site staff (except the unblinded pharmacist responsible for IP preparation and accountability) and the Sponsor (except select sponsor personnel) will be blinded to study treatment allocation and the prophylactic prednisolone/placebo taper, as detailed in Table 10. If additional oral prednisolone (or matching placebo) is administered during or after completion of the taper in response to transaminase elevations, the Investigator will remain blinded as described in Section 7.1.5.

The primary analysis will be performed after the last subject completes the PEAP (Week 48) or an Early Withdrawal Visit. At this time, analyses will be performed using all data from the PEAP and from the safety Follow-up Period at the time of primary database lock. Some Sponsor personnel will be unblinded to treatment groups at the time of this database lock to perform PEAP analysis, but the blind will be maintained for site-facing Sponsor personnel, Investigators, site staff, and subjects until the last subject completes their Week 96 visit.

The final database lock will occur after all subjects complete the 96-week Follow-up Period or Early Withdrawal. At this time, the final analyses will be performed.

Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency, and only when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. To the extent possible before unblinding, the Investigator should contact the Medical Monitor to discuss the medical emergency and the reason for unblinding. The treatment assignment will be unblinded through IRT.

The Investigator is strongly encouraged to contact Ultragenyx before unblinding any subject's treatment assignment, but priority should be given to the safety of the subject.

10. ASSESSMENTS

Parameters to be assessed and the timing of assessments are provided in the Schedules of Events (Table 3, Table 4, Table 5). Protocol waivers or exemptions are not allowed.

Ultragenyx recognizes, based on feedback from PIs and subjects, clinical study participation can be burdensome to subjects. To minimize this burden on subject's mental well-being, independent psychosocial support may be considered by subject's at their own discretion and reimbursed by the Sponsor in accordance with the ICF.

10.1. Data Collection Devices Provided to Subjects

During the Screening Period, subjects (or parents/guardians of pediatric subjects) will be given devices (provided by the Sponsor) to allow electronic data collection.

- A tablet computer that is configured with the following:
  - Patient-reported outcome (PRO) instruments (GSD FAD, PGIS, and PGIC; Section 10.2.5 and Section 10.2.6)
  - The eDiary for recording cornstarch intake, dietary intake, and reason for performing SMBG (if symptomatic) (Section 10.2.1)
  - For subjects < 18 years of age, the subject will complete the PRO instruments on the tablet, and caregivers will be requested to record the subject's cornstarch, dietary intake, and reason for performing SMBG (if symptomatic).
- A Dexcom CGM system (Section 10.2.2) plus a capillary glucometer, test strips, and lancing device for performing capillary glucose controls (ie, SMBG) as instructed
- An internet-compatible laptop for uploading CGM data and SMBG data as described in Section 10.2.2

Study site staff will educate subjects and caregivers on the use of all devices. Subjects will be given training materials to reference at home and should contact the site for additional support as needed (eg, difficulties using the devices or device malfunction).

Subjects will be given a tablet device (provided by assisTek) on which they will complete most PRO assessments (GSD FAD, PGIS, and PGIC) and maintain an eDiary to track daily cornstarch and dietary intake and reason for performing SMBG (if symptomatic). Paper format may be used if eDiary is unavailable or not in use. Entries are to be made by the subject (unless otherwise specified) and are date and time stamped. The subjects and caregivers must authenticate with their security code when they log in to the tablet and they will enter their electronic signatures for each session on the eDiary tablet. The tablets utilize cellular communication to sync to a central study database as soon as entries are completed by the subject. Site staff can monitor subject compliance and will also receive electronic notifications if entries are missed. Additional information and instructions will be provided in the assisTek site and patient user documents.

The CGM devices, laptop computers, eDiary, and blood glucose meters must be returned to the study site after the subject has completed study participation.

10.2. Efficacy Assessments

10.2.1. Assessments of Cornstarch Therapy and Dietary Intake

Subjects will record actual cornstarch intake, including daily frequency and time, as well as other dietary intake routinely throughout the study in a food diary application on the tablet device provided by the study.

Subjects must record their cornstarch and dietary intake in the eDiary daily for at least 4 weeks before the Baseline Visit. During the study and prior to scheduled visits (Weeks 24, 30, 36, 42, 72, 78, 84, 90, 108, 120, 132 and 144/EOS), subjects will record their cornstarch intake daily for at least 1 week before each study visit. Subjects will record their cornstarch intake daily for at least 4 weeks before visits at Week 48 and 96. Subjects will record their daily diet for 3 consecutive days prior to the scheduled visits. Paper format may be used if eDiary is not available. Site staff should contact the subject to remind her/him when to begin daily entries in advance of all applicable scheduled visits. The PI may request additional cornstarch and diet records as needed to assist with nutritional management.

Subjects will also record cornstarch and diet intake and will conduct SMBG (if symptomatic) and record CGM outside the 1 week preceding each visit in accordance with the Investigator's recommendations to ensure safety monitoring of glycemic values (by SMBG) and proceed to modifications of cornstarch following the indications provided in Section 7.1.2. The minimum recommended schedule of assessments for each study period is provided in Table 8.

The Investigator should regularly monitor the prescribed cornstarch regimen and actual amount of cornstarch consumed. Cornstarch and diet prescriptions will not be blinded during the study to the subject or the Investigator. Changes to the cornstarch prescription by the Investigator will be based primarily on blood glucose measurements as detailed in Section 7.1.2. Diet and Cornstarch prescriptions will be recorded in the EDC at screening, baseline, at all study visits, and any time there is a change to the diet or cornstarch prescription.

10.2.2. Capillary Blood Glucose Monitoring

Subjects will be provided a study-approved capillary glucometer, test strips, and lancing device for performing SMBG. It is recommended that subjects take at least 4 SMBG measurements a day (early morning, before two main meals or cornstarch doses, and before bedtime) or as per Investigators recommendation in line with standard of care. It is recommended subjects also take an SMBG when they experience symptoms of hypoglycemia or are in any other situation at risk of hypoglycemia (e.g., delayed meal or cornstarch intake or strenuous exercise). Subjects must perform SMBG at least 4 times daily for at least 4 weeks before the Baseline Visit and for at least 1 week before visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS.

Subjects should bring their glucometer with them to every visit throughout the study.
The Investigator may ask the subject to perform SMBG controls at specific time points based on retrospective reviews of weekly CGM recordings and request that the subject record both the results and the reason for performing SMBG if symptomatic in the eDiary.

10.2.3. Continuous Glucose Monitoring

Continuous glucose levels will be collected using a Dexcom CGM system. The site will provide the CGM system to the subject during the Screening Period. Subjects will be educated on the appropriate care and use of the CGM device and sensors and instructed to wear the CGM device as often as possible and in line with standard of care through the EOS Visit or Early Withdrawal. If a subject's device fatigue makes continuous wear unrealistic, subjects may take a brief break from wearing the CGM, if approved by the treating Investigator or delegate. However, brief breaks in wearing the CGM should not interfere with important protocol prescribed data collection periods noted below. Subjects will be instructed and encouraged to be optimally compliant with wearing the CGM device continuously.

Subjects must wear the CGM device for at least 4 weeks prior to visits at Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132 and 144/EOS. If the required minimum of 4 weeks of consistent data collection is not possible before a planned study visit (eg, due to device technical issues, subject compliance), the Investigator may postpone the study visit to allow for the necessary data collection.

The manufacturer's instructions for the use and care of the CGM device and sensors will be reviewed with the subject and given to the subject for reference at home. Instructions for data transfer to the Sponsor are provided in the training materials. Any deviations from the manufacturer's instructions, such as placement, must be approved and discussed with the Medical Monitor. If the CGM is malfunctioning or the subject cannot use the CGM for any other reason, the subject should contact the study site and coordinate CGM device repair or replacement.

10.2.4. Controlled Fasting Challenge

Cortisol and adrenocorticotropic hormone (ACTH) results must be reviewed by the Principal Investigator to ensure there are no safety concerns that would preclude the clinical trial participant from starting the CFC. Ideally, these assessments will be performed by the institution's local laboratory in a STAT manner. However, in situations where the institutions are unable to perform these assessments STAT, the samples may be drawn between the Randomization and Baseline visit and sent to the central laboratory for analysis or the subject may get these labs drawn at the study site ahead of the Day 0 visit where they can be resulted locally, as long as the results will be available in time for their Day 0 CFC. Subsequent samples for these assessments (ie, during the course of the CFC) may be drawn at the Baseline visit and sent to the central laboratory for analysis and are not required to be processed in a STAT manner (as they are tertiary endpoints and no longer related to assessing continued patient safety or eligibility for dosing).

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

The CFC requires a 24-hour inpatient stay in a hospital or research facility and should be performed after all other study visit assessments are completed and the required laboratory assessments (as specified below) are reviewed by the Investigator (or a Sub-Investigator assigned to review results and make clinical decisions per the site delegation log) prior to the beginning of

the fasting test. Subjects should be wearing their CGM device throughout the fasting challenge, paying attention not to change the sensor prior to the assessment. After dosing and throughout the CFC, an additional CGM device may be used, at the Investigator's discretion, exclusively during CFCs to allow real-time readings of the subject's interstitial glucose concentration and enhance patient safety. This additional CGM device will be connected at the beginning of the CFC and will be immediately removed at the end of the CFC. No data from these readings will be recorded or used alone for clinical decision making. Readings from the unblinded CGM device are meant to alert on a potentially low glucose value during the CFC that would require confirmation by capillary and plasma glucose.

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

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 should be as close as possible to the subject's most current dinner prescription but not higher in carbohydrate content than the dinner of their baseline fasting challenge. Subjects will be encouraged to consume the totality of their dinner. The amount of carbohydrates consumed at the baseline dinner will serve as the basis for calculating subsequent dinners.

Subjects will be instructed to minimize activity after they finish eating dinner until the end of the CFC. Dinner meal start and stop time and its full dietary composition, including the amount of carbohydrates consumed with the dinner meal, will be recorded.

After the dinner meal, subjects will be given an oral dose of cornstarch equivalent to their current cornstarch prescription and schedule. The cornstarch dose should be given within 3 hours of the dinner meal unless otherwise determined by the PI and sponsor. Prior to the start of the CFC, site staff will record the subject's hypoglycemia symptoms on a CFC Questionnaire. The questionnaire should be completed just before the start of the CFC prior to subjects taking their dose of cornstarch. This data will be captured on the appropriate page of the CRF.

The amount of cornstarch to administer should not be higher than what they received at their baseline fasting challenge. Time of cornstarch ingestion and amount of prefasting cornstarch dose consumed will be recorded. The CFC begins after the cornstarch is ingested; start time will be recorded. If a subject does not receive cornstarch before going to bed at the time of the CFC, the fasting challenge should start right after dinner.

During the fast, subjects may drink water, but cannot ingest any other food or drink. The CFC 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 CFC will be recorded.

After the CFC, and where clinically feasible, prior to the subject's meal, site staff will record the subject's hypoglycemia symptoms on a post-CFC Questionnaire while blood draws are being taken. This data along with the time the subject ate their post-CFC meal will be captured on the appropriate page of the CRF. 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 CFC is terminated prematurely before the subject reaches a glucose level of < 54 mg/dL or due to any deviation in the CFC protocol, an ad hoc repeat fasting challenge could be scheduled within 6 weeks from the original date of the CFC.

10.2.4.1. Laboratory Sample Collection Before, During and After the CFC

Prior to Start of the CFC:

- On the morning of the inpatient visit for the CFC, after vital signs and other non-interventional assessments have been performed, cortisol, ACTH, coagulation panel, hematology, and urinalysis samples will be collected in a STAT manner. If the site cannot collect these samples STAT, they should be collected in advance of the visit.
- Standard clinical chemistry (including lipid profiles) will be collected at the time of admission (prior to the CFC) and sent to the central lab. When possible, this sample should be drawn at least 2 hours after the subject's last meal.
- All subjects should have a morning cortisol and adrenocorticotropic hormone (ACTH) measurements prior to their first fasting challenge at baseline. Cortisol and ACTH results should be reviewed by the Investigator or delegate before starting the fasting challenge. Abnormal morning 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 1 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.
- A standard clinical chemistry panel will also be performed at the local laboratory and the Investigator or delegated Sub-investigator must review the results before starting the CFC.

During and After the CFC:

A blood sample 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 within approximately 10 minutes of the beginning of the CFC (as defined earlier in this section) and as soon as possible at the end of the CFC. An additional sample for cortisol, ACTH, growth hormone, and IGFBP1 will be collected approximately 30 minutes (± 10 minutes) after the end of the CFC and after the patient eats their post-CFC meal. This panel may be collected more frequently at the Investigator's discretion. Samples should be prepared and transported to the local laboratory in accordance with the site's standard procedures. In regions where IGFBP1 is not available, this test is optional.

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

- At the beginning of the fast (ie, immediately after the 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 the fast reaches 15 hours without hypoglycemia, whichever occurs first
- At the end of the fast (as soon as possible)
- Approximately 30 minutes (± 10 minutes) after the end of the CFC

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 (especially blood glucose) should be available within 30 minutes after the blood sample collection.

Capillary glucose will be performed at the same time points as the blood samples collected for STAT glucose and lactate at the start, during and end of the CFC. A capillary glucose measurement is not needed for the sample drawn at 30 minutes after the end of the CFC. Capillary glucose can be performed more frequently as needed, and results will be taken at the same time points and will be noted on a CFC results sheet. These data will be used during the PEAP and end of study analyses for corroboration with blinded CGM data recorded during the CFC.

CFC in Pediatric Subjects:

For pediatric subjects weighing < 45 kg, samples other than glucose and lactate are optional and/or per Investigator's discretion based on subject's general status and recent blood counts. When collection is possible and in line with pediatric blood volume limits, assessments which can be resulted using the same collection tube and least amount of blood volume should be prioritized.

10.2.5. Glycogen Storage Disease Functional Assessment Diary

The Glycogen Storage Disease Functional Assessment Diary (GSD FAD) has been developed by Ultragenyx to assess the signs and symptoms of GSD, sleep impacts, and daily impacts experienced by patients with GSDIa.

The GSD FAD consists of a morning and evening diary completed by subjects at the start of the day after waking up regarding the previous night's sleep and at the end of the day regarding their experiences during the day. The morning diary is a 3-item assessment, and the evening diary is a 28-item assessment. Most items consist of a 5-point verbal rating scale. The morning and evening diaries pertain to when they are collected; however, both diaries have items that are integrated to create the scales of the GSD FAD.

There are child/adolescent and adult versions of the GSD FAD and each tablet device will be configured for the appropriate age. Additional instructions will be provided in a separate study manual.

The GSD FAD will be completed electronically by the subject every morning and evening for 14 days prior to the Baseline visit and for 7 days prior to each applicable post-baseline visit. Site

staff should contact the subject to remind them when they need to begin daily GSD FAD entries. Sites will also be notified of noncompliance and will contact the subjects if entries are missed.

In addition, a paper-based, weekly version of the GSD FAD that applies a 7-day recall to the items will be completed by subjects at the applicable visits to evaluate the equivalence of the daily eDiary GSD FAD and the weekly GSD FAD.

10.2.6. Patient Global Impression of Change and Patient Global Impression of Severity Measures

Patient global impression of change (PGIC) and Patient Global Impression of Severity (PGIS) items assess health status from the patient perspective and are commonly used in clinical trials to evaluate the patient perspective of treatment efficacy. The PGIC uses a 7-point response continuum to capture the patient perspective on changes in their GSDIa since the start of the study. The Patient Global Impression of Change – Cornstarch Treatment Tolerance (PGIC-CTT) items use a 7-point response continuum to capture the patient perspective of changes in gastrointestinal symptoms associated with cornstarch use since the start of the study. The PGIS items use a 5-point response continuum to capture patient perspectives on frequency of low blood sugar, overall health status, severity of GSDIa symptoms, and bother by GSDIa impacts.

The PGIC and PGIS will be completed electronically via the eDiary on the day before each applicable study visit,. The PGIC will be administered once during the Screening period, will not be administered at the Baseline Visit, and will be administered at post-baseline visits as indicated in the Schedule of Events. The PGIS will be administered twice during the Screening Period and once at the Baseline Visit (Day 0), and at post-baseline visits as indicated in the Schedule of Events. If PGIC and/or PGIS data have not been reported in the eDiary preceding the applicable study visit, the clinic site staff will have the subject complete the PGIC and/or PGIS on paper at the time of the study visit. The PGIC-CTT will be collected on paper at each applicable study visit, following the post-baseline visits as indicated in the Schedule of Events.

There are child/adolescent and adult versions of the PGIC and PGIS, and each tablet device will be configured for the appropriate age. Additional instructions will be provided in a separate study manual.

10.2.7. EQ-5D-5L/EQ-5D-Y

The EQ-5D-5L is a brief assessment that is composed of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and is rated on a 5-point rating scale to indicate the level of impairment. In addition to the EQ-5D-5L, there is a pediatric version, the EQ-5D-Y, that can be administered to subjects below the age of 18.

The EQ-5D-5L/EQ-5D-Y will be completed on paper at the site, during the applicable study visit, before any invasive assessments are conducted. Study staff should review the forms for completeness once the subject returns the forms to staff. Data collected on the EQ-5D-5L/EQ-5D-Y will be captured on the appropriate page of the CRF.

10.2.8. Health Economics Outcomes Research Assessments

Medical Resource Utilization

- Medical resource utilization will be collected via a questionnaire. The purpose of the survey is to collect real-world data to understand economic burden of disease, specifically hospitalization (length-of-stay [LOS] in hospital, LOS in intensive care unit) and emergency room visits, outside of those required for participation in the trial.

Work and School Status and Absenteeism

- The impact of disease on productivity, specifically absenteeism from work or school, will be assessed by a questionnaire. The goal will be to understand impact of disease on absenteeism. Work and school status will be asked of the subject and caregiver. Work productivity will be assessed by the World Health Organization (WHO) Health Productivity Questionnaire (HPQ) short version (Kessler et al., 2003). Absenteeism and presenteeism will be calculated based on WHO HPQ scoring guidelines.

Detailed instructions will be provided in a separate study manual.

10.2.9. Entry and Exit Interview

Subjects will be asked to complete an interview between randomization and dosing to better understand their experience with GSDIa prior to IP administration. These subjects will be asked to complete a brief telephone interview at Week 48 and Week 96 to explore their experiences 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 Outcomes uses a semi-structured script as an interview guide to serve as a basis for the discussion. The interview can be conducted in phone or in-person and will be audio recorded and transcribed for analysis.

10.3. Biomarker Assessments

10.3.1. 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 confirm the presence of a *G6PC* mutation. However, as molecular methods have evolved in the last few years, *G6PC* mutation analysis will not be waived for any participant unless results have been obtained from the same laboratory conducting the analysis for the study and are available in the study subjects' medical records.

10.3.2. Urinary Hex4 Assessments

Urinary tetra glucose (Hex4) Glc4 is the only available biochemical biomarker of disease burden for other GSDs including GSD II (Pompe disease) and more recently GSDIII. This biomarker is easily measurable in urine by MS/MS. A sample from the 24-hour urinary collections performed

at baseline and before or during certain inpatient visits will be used for this assessment. Analysis will be performed in a central laboratory.

10.3.3. Optional Blood and Urine Collection for Future Exploratory Use

Optional blood and urinary samples for DTX401-related exploratory future research may be collected at specified time points. Optional blood collection may be performed for subjects who consent to sample collection for exploratory future research, if this sample would not exceed maximum blood sampling volume. Urine samples may be collected from the 24-hour urine collection performed at baseline and certain inpatient visits.

10.4. Safety Assessments

Safety will be evaluated by the incidence, and severity of treatment-emergent AEs and SAEs and by changes from study baseline to scheduled time points in vital signs, weight, electrocardiograms, physical examination, clinical laboratory evaluations, imaging procedures, and concomitant medications. Pregnancy testing (or pregnancy testing of partner, if needed) will also be conducted.

Safety definitions and instructions for assessing severity and causality are presented in Appendix 4.

Appendix 5 provides instructions regarding how to elicit, record, and report collection period timeframes and timelines for AEs, SAEs, pregnancies, other safety information and any urgent safety measures taken to protect the safety or welfare of subjects.

10.4.1. Adverse Events of Special Interest

Vector-induced hepatic effects are considered to be adverse events of special interest (AESIs) for this study and are defined as clinically significant increases in aminotransferase levels in the medical and scientific judgment of the Investigator following IP administration. Clinically significant increases in aminotransferase levels have been observed across various AAV gene therapy clinical studies in multiple indications.

All AESIs should be reported to Ultragenyx as AEs or SAEs, with severity and causality, as outlined in Appendix 4 and Appendix 5.

In clinical studies with AAV gene therapy, mild, transient, asymptomatic increases in liver aminotransferase levels and a concurrent decline in transgene expression have been observed following AAV vector administration (Nathwani et al., 2014; Nathwani et al., 2011; Manno et al., 2006). These increases in liver aminotransferase levels have been shown to resolve with reactive corticosteroid administration (Derks et al., 2019; Weinstein et al., 2019). More recently, prophylactic corticosteroid administration has been introduced to prevent possible vector-induced hepatic effects in AAV gene transfer clinical trials in other indications (Clinicaltrials.gov identifiers: NCT02716246, NCT03223194).

To minimize or prevent potential vector-induced hepatic effects (eg, increased aminotransferase levels) and the concurrent decline in transgene expression, subjects who receive DTX401 (Derks et al., 2019) will receive prophylactic oral corticosteroids as described in Section 9.2. Additional oral corticosteroids may be administered following completion of the prophylactic corticosteroid regimen if a subject's ALT levels increase from baseline or recently tested levels and the

Investigator considers the increase to be possibly related to treatment with IP. Based on available evidence, it is expected that any vector-induced hepatic effects will be self-limited.

Clinical chemistry, including liver function tests, will be assessed before and after IP administration and frequently throughout the duration of the study. Blood cortisol levels will be measured before initiation of and during prophylactic corticosteroid administration. Treatment with prednisolone is associated with risks including fluid retention, altered glucose tolerance, weight gain, hypothalamic-pituitary-adrenal (HPA) axis suppression, infections, hypertension, behavioral/mood disturbances, decreased bone density. Risks associated with prednisolone treatment will be monitored by the Investigator during study visits and phone calls to subjects at the time of the prednisolone/placebo regimen (Section 9.2). Adrenal insufficiency is considered a potential risk of study-related procedures and is an AESI. At any time after initiation of prophylactic corticosteroids, laboratory assessments may be completed to assess clinical status and subject safety at the Investigator's discretion and as clinically indicated.

Infusion-related reactions (IRRs) including hypersensitivity are considered an AESI for DTX401. IRRs with features of hypersensitivity have been observed with blinded IP in this trial, including anaphylaxis. IRRs for this study are defined as adverse events with features of hypersensitivity with onset during the infusion or up to 6 hours after end of the infusion.

IRRs may be allergic (anaphylactic) and mediated by IgE or may be nonallergic and not mediated by IgE. Regardless of whether they are allergic or nonallergic, the clinical manifestations may be similar and require prompt, accurate assessment and astute management to avoid severe outcomes (Vogel, 2010). Symptoms of IRRs range from mild to severe or life-threatening and may include headache, myalgia, pruritis, urticaria, fever, flushing, diaphoresis, gastrointestinal symptoms (abdominal pain or cramping, vomiting), bronchospasm, hypotension, angioedema and anaphylaxis.

Potential IRRs are managed with pre-medication, slow and staged infusion of blinded IP with clinical staff experienced in management of infusion-related reactions, close and continuous monitoring for infusion reactions and subject and parent/guardian education on signs and symptoms of allergic reactions at discharge. Refer to Section 5.5 for risk minimization for possible infusion reactions and Section 9.1.4 for clinical observation and supportive care.

All AESIs should be reported to Ultragenyx as AEs or SAEs, with severity and causality, as outlined in Appendix 4 and Appendix 5.

10.4.2. Severe Hypoglycemic Events

A severe hypoglycemic event (SHE) is defined as an episode with signs/symptoms of neuroglycopenia such as ataxia, dizziness, drowsiness, confusion, delirium, loss of consciousness, seizure or coma requiring assistance from a third party or medical intervention, and where the patient had one of the following characteristics: (i) blood glucose ≤54 mg/dL recorded by CGM and/or capillary blood glucose measurement, or (ii) reversal of symptoms after food intake or IV glucose administration. If a SHE occurs, the site is to report the SHE as an SAE to the Sponsor, within 24 hours of awareness, with the term "Neuroglycopenia."

10.4.3. Vital Signs

Vital signs to be measured include seated systolic blood pressure and diastolic blood pressure, heart rate, respiration rate, and temperature.

On the day of IP administration, vital signs will be collected as detailed in Section 9.1.4. At other study visits, vital sign measurements will be performed before any additional assessments are completed.

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.

Changes from study baseline considered to be clinically significant in the medical and scientific judgment of the Investigator will be recorded as AEs or SAEs.

10.4.4. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT intervals.

ECGs should be performed after the subject has rested for at least 5 minutes. If the subject is not sufficiently rested, this needs to be stated in the source documents.

10.4.5. Physical Examinations

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

A targeted physical examination will include, at a minimum, assessments of the skin, abdomen with documentation of liver and spleen size, and respiratory, cardiovascular, and gastrointestinal systems. Tanner pubertal stage development will be assessed at baseline and in all postdosing inpatient visits for pediatric subjects < 18 years (Appendix 7).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

10.4.6. Liver Ultrasound

An ultrasound of the liver will be conducted during screening and at Week 36 and Week 96 (or Early Withdrawal) to analyze liver parenchyma and confirm the presence of and, if present, the size of an adenoma. At the investigator's discretion, an alternative imaging modality, e.g. CT or MRI, can be used in place of liver ultrasound if more clinically appropriate.

10.4.7. Safety Laboratory Tests

The clinical laboratory evaluations to be performed in this study include clinical chemistry, hematology, coagulation panel, and urinalysis. Standard clinical laboratory assessments are listed in Table 19.

Samples for clinical chemistry should be collected after vital signs and other noninterventional assessments have been performed, and at least 2 to 4 hours after the subject's last meal. On days when the CFC will be performed, clinical chemistry samples will be sent to both the central and local laboratories. Results from the local laboratory must be reviewed before starting the CFC or before IP administration. Details for the preparation and shipment of samples will be provided by the central or specialty laboratory, as applicable. Reference ranges for all parameters will be provided to the study site in the Laboratory Manual.

On the day of IP administration, a blood sample for analysis of clinical chemistry (including LFTs) will be collected approximately 0.5 and 2 hours after the start of the IP infusion and sent to the local laboratory. Additional blood samples for clinical chemistry may be collected during the post-IP infusion observation period if clinically indicated. The Investigator should review the laboratory results before the subject is discharged.

Unscheduled home health visits may be scheduled at the Investigator's discretion for safety purposes. Blood collection may be performed at home healthcare visits arranged by the study site or at the study site, according to local medical practice and/or subject preference.

Blood collection may be decreased for pediatric subjects through microsampling and/or prioritizing the collection of key samples. The general rule for prioritizing is: safety labs, labs contributing to the primary and secondary endpoints, labs related to tertiary endpoints, research samples. Further details on blood collection volume limits are provided in the Laboratory Manual.

Laboratory tests 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, including those that worsen from baseline or those considered clinically significant in the medical and scientific judgment of the Investigator, are to be recorded as AEs or SAEs (Appendix 5). However, any clinically significant laboratory results that are associated with GSDIa should not 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 values. If results do not return to normal within a period judged reasonable by the Investigator, the etiology should be identified and the Sponsor should be notified.

The clinical laboratory evaluations to be performed in this study are listed in Table 19.

For any subject who experiences an SAE or other AE of concern, the Investigator (and/or Medical Monitor) may at his/her discretion perform additional laboratory tests for subject safety. Only clinically significant symptomatic hypoglycemic (<60 mg/dL) events (e.g. reported from eDiary, CGM, or SMBG report), in the opinion of the Investigator, are to be recorded as "Hypoglycemia" on the adverse event electronic case report form. For reporting severe hypoglycemic events (SHE), refer to Section 10.4.2.

10.4.8. 24-Hour Urine Collection

The excretion of total protein, microalbumin, creatinine, and Hex4 in the urine will be determined over a 24-hour period. Timed 24-hour complete urine samples will be collected over the 24-hour period preceding scheduled visits. Appropriate collection kits will be provided by the

central laboratory and a single pooled sample will be shipped to the central laboratory. Details are provided in the 24-hour Urine Collection Instructions worksheet.

10.4.9. Pregnancy Testing

Female subjects of childbearing potential will have a serum pregnancy test at screening. Female subjects not of childbearing potential are not required to undergo pregnancy testing. Refer to Appendix 3 for childbearing potential definitions.

Female subjects with a positive pregnancy test at screening will not be enrolled in the study.

Urine pregnancy tests will be performed throughout the study as indicated in the Schedule of Events. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result or can be performed if pregnancy test by urine is not feasible.

If a subject becomes pregnant on study or a partner of a male subject becomes pregnant, the treatment assignment of the pregnant subject or the male subject will be unblinded.
The Investigator must then contact the Medical Monitor to determine options for continued monitoring in the study.

Refer to Appendix 5 for pregnancy reporting requirements. Contraception guidance is provided in Appendix 3.

10.4.10. Concomitant Medications

Medications (investigational, prescription, over-the-counter, and herbal supplements) vaccinations and nutritional supplements taken during the 30 days prior to screening will be reviewed and recorded at the Screening Visit. Use of any concomitant medications during the study should be recorded on the CRF. All concomitant medications will be coded according to the WHO Drug Dictionary.

Site personnel should record the date the medication was taken, name of the medication, medication dosage, formulation, route of administration, and reason the medication was taken.

10.4.11. Safety Follow-up With Subject's Health Care Provider

With the subject's written consent and when possible, the site may communicate directly with the subject's HCP (ie, primary care physician or their designee) throughout the study to collect health status information and AEs, in accordance with relevant patient privacy laws.
The Investigator should contact the subject's HCP within 30 days of the subject's consent to participate in the study to establish a process for communicating health status information, including frequency, and method of contact.

Throughout the study, the site will contact the subject's HCP as frequently as necessary. During these contacts, the Investigator will ask the HCP about any AEs or changes in the subject's health status since the last contact. The Investigator will also inform the subject's HCP to contact the Investigator at any time with any safety concerns and to report any AEs or changes in the subject's health status to the Investigator if they occur. If a subject withdraws consent to participate in the study, the site may continue to contact the subject's HCP or review available public information to determine the subject's survival status. If a subject dies during the study,

an autopsy may be requested to assess DTX401 vector persistence, transgene expression, and related adverse reactions at the tissue, cellular, or molecular level.

The Investigator is responsible for reporting all AEs and SAEs to Ultragenyx in accordance with Appendix 4 and Appendix 5.

10.5. Immunogenicity Assessments

10.5.1. AAV8 Total Antibody Assay

A blood sample will be collected for the AAV8 TAb assay at the time points specified in the Schedule of Events. This investigational use only AAV8 TAb assay detects antibodies to AAV8. It is recommended that the screening sample be collected at the time written informed consent is provided; the presence of detectable pre-existing antibodies to the AAV8 capsid would exclude a subject from study participation and the subject would not be eligible for rescreening.

Subjects who receive placebo on Day 1 will not be able to receive DTX401 at Week 48 if their Week 36 AAV8 TAb results indicate development of antibodies to AAV8. In this case, the subject and the Investigator will be notified after the Week 48 assessments are complete and before any Year 2 activities begin. The subject will withdraw from the study once all Week 48 assessments are completed. Investigators will not receive the Week 36 AAV8 TAb results for other subjects who are continuing in the study for the extension phase in order to maintain the blind. The unblinded Clinical Trial Manager (overseeing the pharmacy monitor) will review results from the Week 36 AAV8 TAb assay for eligibility for IP administration at Week 48. The Investigator will review the Week 42 assessments as soon as they are available as well as Study Continuation Criteria to confirm that the subject is eligible to receive IP administration at Week 48. If there is evidence of any change from baseline in disease status or overall well-being that would preclude safe administration of DTX401, the Investigator will consult the Medical Monitor.

Positive AAV8 TAb assay samples will be further analyzed with the AAV assay (immunogenicity assay) for future DTX401-related research. Results will not be provided to sites. Instructions for collecting, preparing, and shipping samples are provided in the Laboratory Manual.

10.5.2. Cell-mediated Immune Response

The presence of T cells specific for G6Pase will be determined by an enzyme-linked immunospot (ELISpot) assay. A blood sample will be collected at the time points specified in the Schedule of Events (Table 3 and Table 4). In order to maintain the blind, anti-G6Pase antibody test results will not be made available to the Investigator before the end of the study. Ad-hoc assessments may be performed following requests from CIC and DMC. For pediatric subjects weighing < 45kg, assessments at Week 6 and Week 54 are optional and/or per Investigator's discretion based on subject's general status and recent blood counts. Efforts should be made to collect as frequently as is possible without exceeding pediatric blood volume limits.

10.5.3. AAV8 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 3 and Table 4) to monitor for circulating anti-AAV8

antibodies. The assay will be performed using a validated method. Subjects who receive DTX401 will develop AAV8 antibodies and this assessment will measure the level of the immune response after treatment with DTX401. The results will remain blinded to the Investigator until the end of the study. For pediatric subjects weighing < 45kg, assessments at Weeks 4, 6, 24, 52, 54, and 72 are optional and/or per Investigator's discretion based on subject's general status and recent blood counts. Efforts should be made to collect as frequently as is possible without exceeding pediatric blood volume limits.

10.5.4. Anti-Glucose-6-Phosphatase Antibody Assay

Serum samples for the anti-G6Pase antibody assay will be collected at the time points specified in the Schedule of Events to detect the presence of circulating anti-G6Pase antibodies.
This immunogenicity assay will be performed using a validated method. In order to maintain the blind, anti-G6Pase antibody test results will not be made available to the Investigator before the end of the study.

10.5.5. Complement Assessments

Samples to assess complement (C3, C4, SC5b-9, CH50, AH50, MBL) will be taken prior to blinded IP administration as shown in Table 3. If a subject experiences an infusion-related reaction, these labs should be measured 30 to 120 minutes after the start of the reaction, and once again at least 24 hours after the symptoms have resolved. The timing of sample collection should be documented.

If there are challenges in obtaining blood samples, the order of sampling priority is 1) tryptase, C3, C4, and CH50, 2) AH50 and MBL, and 3) SC5b-9.

10.5.6. Serum Tryptase Assessment

A serum sample will be drawn in all subjects prior to dosing with blinded IP as shown in Table 3. If a subject experiences an infusion-related reaction, serum tryptase should be measured 30 to 120 minutes after the start of the reaction, and once again at least 24 hours after the symptoms have resolved. The timing of sample collection should be documented.

10.6. Appropriateness of Measurements

The proposed primary and secondary endpoints in Phase 3 are designed in a complementary manner to report efficacy outcomes that explore multiple facets of GSDIa physiology and are tied to subjects reporting their own perceived clinical benefit, such as greater mental clarity, more energy, and weight loss. The significant decrease in daily disruptions to subjects' daily lives from a professional, academic, and social standpoint must not be underestimated. There is also an element of convenience and safety for subjects when they are no longer required to travel with, or require ready access to, excessive containers of cornstarch and water for their recurrent rescue therapy treatment.

When assessing all components of subjects' disease experiences after DTX401 treatment, a reduction in cornstarch intake while maintaining or improving glycemic control supports clinical meaningfulness from the subjects' and Investigators'/treating physicians' perspectives.
The Phase 3 study is expected to provide a robust assessment of the efficacy of DTX401 to

provide a more physiologic treatment of GSDIa and thereby address the high unmet medical need and reduce the disease burden in these patients.

Electronic capture of key data (eg, CGM, capillary glucose [SMBG], eDiary for cornstarch and dietary intake, electronic PRO questionnaires) is intended to encourage thorough, efficient, and accurate reporting by subjects/caregivers.

11. STATISTICAL CONSIDERATIONS

A full description of the analysis details will be provided in the Statistical Analysis Plan (SAP).

11.1. Sample Size Determination

The study will enroll approximately 50 subjects with 25 subjects randomly assigned to the DTX401 Group and 25 subjects randomly assigned to the Placebo Group in a 1:1 ratio. Randomization will be stratified by age (< 18 years vs ≥ 18 years) and baseline percentage of values in the target blood glucose range of 60 to 120 mg/dL (<60%, ≥60% and ≤85%, >85%).

For the primary endpoint (Section 11.3.2.1), a sample size of 50 subjects (25 subjects in the DTX401 Group, 25 subjects in the Placebo Group) will provide approximately 91% power to detect a difference between the DTX401 Group and the Placebo Group at Week 48 using MMRM including repeated measures at Week 24, Week 30, Week 36, Week 42, and Week 48 at 0.05 alpha. This assumes a minimum average cornstarch reduction of 50% or more in the DTX401 Group at Week 48 versus a maximum average of 10% cornstarch reduction or less in the Placebo Group at Week 48 with a common SD of 40%, a correlation coefficient of 0.4 between assessments, and a discontinuation rate of 10% at Week 48.

11.2. Analysis Sets

For the purposes of analysis, the analysis sets are defined in Table 15.

In this study, there is a minimum of 10 days between randomization and IP administration due to the time required to ship IP (DTX401/placebo) and prednisolone/placebo kits to the investigational site. Therefore, it is possible that a few subjects may not receive IP after being randomized (eg, if the subject decides to withdraw from the study or due to some unforeseen circumstance).

Table 15: Planned Analysis Sets

Analysis Set	Description
Intention-to-Treat (ITT)	Includes all randomized subjects who received any IP (DTX401 or Placebo). Analysis will be performed based on the randomized treatment in this study.
Modified Intention-to-Treat (mITT)	Consists of all randomized subjects who received any IP (DTX401 or Placebo) and provided at least one post-dosing assessment pertaining to primary efficacy analysis (i.e., at least one assessment of daily cornstarch intake corresponding to the visits at Weeks 24, 30, 36, 40, 42, and 48). Analysis will be performed based on the randomized treatment in this study. All efficacy analyses will be performed on the mITT set. If all randomized subjects receive IP and provide at least 1 post-dosing assessment pertaining to primary efficacy analysis, all efficacy analyses will be performed on the ITT set as described above.
Per Protocol Set (PPS)	Excludes mITT subjects with any major protocol violations that may impact the primary and secondary efficacy analyses. The exclusion of subjects from the PPS population will be determined in a final blinded data review meeting that will be held prior to the disclosure of the randomization list. Reasons for exclusion will be documented for each subject. The primary and secondary efficacy endpoints will be performed on the PP population to support the primary analyses.

Analysis Set	Description
Safety (SAF)	Consists of all subjects treated with study IP. Subjects will be analyzed based on the actual treatment received. The safety analysis will be performed using the SAF.

11.3. Planned Methods of Analysis

11.3.1. General Principles

A general description of the statistical methods to be used to analyze the study endpoints is outlined below. The analyses planned in this protocol will be expanded in the SAP to include detailed descriptions of the analyses.

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. Continuous variables will be summarized by number of subjects and mean, SD/standard error, Q1, Q3, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

The safety and efficacy analyses will be presented by study periods. For the PEAP, summary tabulations will be provided by DTX401 and Placebo. For the Follow-up Period, summary tabulations will be provided by DTX401->Placebo and Placebo->DTX401.

All statistical tests will be 2-sided and tested at the significance level of 0.05. Adjustment for multiplicity of testing will be performed on 3 secondary efficacy endpoints with methods assuring the formal control of the Family Wise Error Rate at a strict 5% level of significance. The multiplicity adjustment methods to be used are fully described in Section 11.3.2.5. Summary statistics will be presented, as well as confidence intervals on selected parameters.

11.3.2. Efficacy Analyses

11.3.2.1. Primary Efficacy Endpoint

The primary endpoint is the percent change from Baseline to Week 48 in daily cornstarch intake for the DTX401 Group compared with the Placebo Group. The hypothesis for this endpoint is:

H0: Percent change from Baseline to Week 48 in daily cornstarch intake in DTX401 Group is the same as percent change from Baseline to Week 48 in daily cornstarch intake in Placebo Group

H1: Percent change from Baseline to Week 48 in daily cornstarch intake in DTX401 Group is different than percent change from Baseline to Week 48 in Placebo Group

The percent change in daily cornstarch intake at Week 48, will be evaluated using MMRM, taking into account cornstarch intake at Baseline, stratification factors, the treatment group, study visit (last 5 scheduled visits: Weeks 24, 30, 36, 42, and 48), and interaction of visit by treatment as covariates. For each visit, data on daily cornstarch intake over 1 week prior to the visit will be used; except for visits at Baseline and Week 48 where data over 4 weeks prior to the visit will be used.

Descriptive summary statistics will be reported for each treatment group for the following subcategories of cornstarch reduction from baseline: $< 50\%$, $\geq 50\%$, $\geq 70\%$, $\geq 90\%$, and 100%.

Plots by study visits will be presented by treatment group for the primary efficacy analyses. The primary efficacy analysis will be repeated on the PP set for sensitivity purpose.

Further, clinical meaningfulness of the primary endpoint will be supported with a supplementary responder analysis based on a ≥ 50% reduction in cornstarch quantity (ie, subject with daily cornstarch reduction ≥ 50% from baseline to Week 48 will be considered as a responder). Responder rates will be compared using the Cochran-Mantel Haenszel (CMH) test using stratification factors. Additionally, cumulative distribution function (CDF) plots of responses for the DTX401 and placebo group showing percent change from baseline to Week 48 in daily cornstarch on the X-axis and the percent of patients experiencing that change on the Y-axis will be provided.

11.3.2.2. Secondary Efficacy Endpoints

Secondary Efficacy Endpoints Adjusted for Multiplicity

The following 3 secondary endpoints will be formally tested with multiplicity adjustment. (The multiplicity adjustment methods to be used are fully described in Section 11.3.2.5):

- Change from Baseline to Week 48 in number of total daily doses of cornstarch (DTX401 vs placebo)
- Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (<70 mg/dL [3.9 mmol/L]) assessed for non-inferiority (DTX401 vs Placebo); if non-inferiority is met, this endpoint will be tested for superiority. However, superiority will not be adjusted for multiplicity.
- PGIC assessment score at Week 48 (DTX401 vs Placebo)

Changes from Baseline to Week 48 in number of total daily doses of cornstarch intake in DTX401 Group and Placebo Group will be analyzed using MMRM including Baseline, stratification factors, the treatment group, study visits (Weeks 24, 30, 36, 42 and 48), and interaction of visit by treatment as covariates. The estimation of the Week 48 contrast (DTX401 − Placebo) will provide the Least Squares Mean and the 95% confidence interval of the estimated difference between DTX401 and Placebo. Descriptive summary statistics of changes in daytime doses of cornstarch and nighttime doses of cornstarch (doses that disrupt the regular night sleep pattern of the subject) in each treatment group will be reported.

Change from Baseline to Week 48 in percentage of glucose values in the hypoglycemic range (<70 mg/dL [3.9 mmol/L]) will be analyzed using both CGM and SMBG data. Details of the analyses will be included in the SAP. The analysis method will be MMRM including Baseline percentage of values in the hypoglycemic range, stratification factors, the treatment group, study visits (Weeks 24, 30, 36, 42 and 48), and interaction of visit by treatment as covariates. The estimation of the Week 48 contrast (DTX401 − Placebo) will provide the Least Squares Mean estimate of the difference between DTX401 and Placebo. The p-value for the non-inferiority test will be calculated and used in the Hochberg procedure. Further, (1-α/2)100% 1-sided confidence interval for the difference in mean reduction in percent of values in hypoglycemic range between DTX401 and Placebo will be calculated where α is determined by the Hochberg procedure. Statistical non-inferiority will be demonstrated if a lower bound of that confidence interval is greater than the non-inferiority margin (as specified in the SAP). Only if non-inferiority is

established, superiority will be tested at 0.05 alpha. The endpoint of superiority will not be adjusted for multiplicity.

PGIC score at Week 48 will be analyzed using MMRM including stratification factors, the treatment group, study visits (Weeks 24, 36, and 48), and interaction of visit by treatment as covariates. The estimation of the Week 48 contrast (DTX401 − Placebo) will provide the Least Squares Mean and the 95% confidence interval of the estimated difference between DTX401 and Placebo.

Other Secondary Efficacy Endpoints

Change from Baseline to Week 48 in time to hypoglycemia (< 54 mg/dL [< 3.0 mmol/L]) during the CFC in DTX401 Group and Placebo Group will be analyzed using MMRM including Baseline time to hypoglycemia, stratification factors, the treatment group, study visits (Weeks 36 and 48), and interaction of visit by treatment as covariates. Time to hypoglycemia at Baseline is defined as the time to hypoglycemia during the CFC performed at Day 0. The mean time to hypoglycemia and the mean change from Baseline at all scheduled assessment time points will be summarized by treatment group. The p-value for the comparison and the 95% confidence interval for the estimated difference between DTX401 and Placebo will be provided based on the MMRM model described above.

Change from Baseline to Week 48 in percentage of glucose values in the range of 70 to 120 mg/dL [3.9 to 6.7 mmol/L]) will be analyzed using both CGM and SMBG data. Details of the analyses will be included in the SAP. The analysis method will be MMRM including Baseline percentage of glucose values in 70-120 mg/dL range, stratification factors, the treatment group, study visits (Weeks 24, 30, 36, 42 and 48), and interaction of visit by treatment as covariates. The estimation of the Week 48 contrast (DTX401 − Placebo) will provide the Least Squares Mean estimate of the difference between DTX401 and Placebo. One-sided 97.5% confidence interval for the difference between DTX401 and Placebo will be calculated. Statistical non-inferiority will be demonstrated if a lower bound of that confidence interval is greater than the non-inferiority margin (as specified in the SAP). Only if non-inferiority is established, superiority will be tested at 0.05 alpha. The p-value for the comparison and the 95% confidence interval for the estimated difference between DTX401 and Placebo will be provided based on the MMRM model described above.

11.3.2.3. Tertiary Efficacy Endpoints

For each of the continuous tertiary endpoints, MMRM will be used to analyze the change from Baseline to Week 48. The contrast between groups at Week 48 will provide the least squares mean and 95% confidence interval corresponding to the comparison of interest, for exploratory purpose. For categorical endpoints, the CMH test will be used and estimate of treatment difference and 95% confidence interval for the estimated difference will be reported for exploratory purposes.

11.3.2.4. Planned Subgroup Analyses and Sensitivity Analyses

Subgroup analyses may be performed in pediatric subjects according to pubertal stage for the primary and secondary endpoints (if sample size allows).

Subgroup analyses will be performed for the primary and secondary endpoints by stratification factors.

Sensitivity analyses will also be performed in the primary endpoint to address the potential impact from the intercurrent events (e.g., transient changes in dietary management or nutritional intake due to acute events, such as trauma, surgery, infection, metabolic decompensation, etc.; sub-acute changes in glucose homeostasis due to adjustments in corticosteroid dose or other medications affecting glucose homeostasis, such as insulin; persistent changes in dietary management or nutritional intake due to intentional or foreseeable physiologic changes, such as seasonal changes in activity, a new weight loss regimen, exercise program, puberty, pregnancy, etc.) on the estimands. For the primary analysis, the treatment policy (ITT approach) will be applied. In the sensitivity analysis, the data at visits impacted by the intercurrent event will be set to missing and the results will be imputed based on the method described in the SAP. For the primary endpoint analysis, the estimand, estimators, and primary approach to address intercurrent events are described in Table 16.

Table 16: Estimand, Estimators, and Primary Approach to Address Intercurrent Events for Primary Endpoint

Estimand Attributes	Estimator and Estimate	Primary Strategy to Handle Intercurrent Events
• Treatment: Subjects randomized to DTX401 vs Placebo • Population: Adults and pediatric subjects ≥ 8 years of age with GSDIa • Variable (Endpoint): Percent change from Baseline to Week 48 in daily cornstarch intake • Population-level Summary: The difference in mean percent change from Baseline between the two treatment arms at Week 48	Estimator: • Difference in mean percent change from Baseline at Week 48 between DTX401 and placebo Estimate: • Difference (DTX401 and Placebo) of least squares mean of percent change from baseline in daily cornstarch intake at Week 48 estimated by MMRM model	• Follow the ITT principle (treatment policy approach)

11.3.2.5. Multiple Comparisons/Multiplicity

If the primary endpoint is met, the following 3 secondary endpoints will be compared between the 2 treatment groups (DTX401 vs placebo) and will be formally tested using a Hochberg method (Table 17) based on the rank order of the p-values.

- Change from Baseline to Week 48 in number of total daily doses of cornstarch (DTX401 vs placebo)
- Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (<70 mg/dL [3.9 mmol/L]), assessed for non-inferiority (DTX401 vs Placebo); if non-inferiority is met, this endpoint will be tested for superiority. However, superiority will not be adjusted for multiplicity.
- PGIC assessment score at Week 48 (DTX401 vs Placebo)

Table 17: Hochberg Method (3 Endpoints)

	p value	Significant	p value	Significant	p value	Significant
Endpoint (1)	≤ 0.05	Yes	> 0.05	No	> 0.05	No
Endpoint (2)		Yes	≤ 0.025	Yes	> 0.025	No
Endpoint (3)		Yes		Yes	≤ 0.0167	Yes

Note: Endpoints are ranked by p values from (1) to (3) from the largest to the smallest.

11.4. Safety Analyses

Safety variables, including all AEs, SAEs, safety laboratory assessments, vital sign measurements, and electrocardiograms (ECGs), will be summarized by treatment group.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or later. The frequency and severity of all TEAEs, treatment-emergent SAEs, and AESIs will be reported by system organ class (SOC), preferred term (PT), and relationship to study drug, as applicable. All AEs reported with onset after IP administration (ie, TEAEs) will be included in the safety analysis. All treatment-emergent SAEs will also be reported by relationship to study drug as reported by Investigator, seriousness, and outcome. For all TEAEs and treatment-emergent SAEs, the percentage of subjects who experienced at least 1 occurrence of the given event will be summarized by treatment group. Data summaries and/or listings and narratives will be provided for subjects who died, discontinued treatment or withdrew from study due to an AE, or experienced SAEs and any study procedure-related AEs.

Clinical laboratory data will be summarized by the type of laboratory test and by changes from baseline. Reference ranges and abnormal results will be used in the summary of laboratory and ECG data. The frequency and percentage of subjects who experience abnormal clinical laboratory results (ie, outside of reference ranges) will be presented for each clinical laboratory measurement. Shift tables will be provided for changes from baseline in selected chemistry and hematology laboratory parameters (if applicable). Listings of abnormal vital signs will be provided (if applicable). The SAP will provide additional details on the planned safety analyses.

11.5. Other Analyses

The following immune response parameters will be summarized descriptively by visit and treatment group and/or provided in listings:

- Blood sample collection for presence of antibodies to the AAV8 capsid and anti-G6Pase antibodies
- Cell-mediated immune response to G6Pase (ELISpot)

GSDIa genotype:

- GSDIa genotyping results during Screening

COVID-19:

- COVID-19 contingency measures and study participants affected by COVID-19 will be listed

11.6. Planned Analyses

Analyses of all primary, secondary, and tertiary endpoints will be performed after all subjects have completed the Week 48 Visit. Further analyses will be performed after the last study participant has completed the Week 96 visit and after the last study participant has completed the Week 144/EOS or Early Withdrawal Visit. No interim analyses are planned.

11.7. Study Oversight Committees

Study oversight is provided by an unblinded, independent DMC and an unblinded CIC. Further details regarding the DMC and CIC can be found in each committee's charter.

11.7.1. Data Monitoring Committee

An independent DMC including 2 clinicians and 1 statistician will be constituted for Study DTX401-CL301 and will act in an advisory capacity to provide safety oversight and to monitor subject safety on a routine basis throughout the course of the study.

The DMC will meet and review study data at the frequency defined and in accordance with the scope and objectives set forth in the DMC Charter. The DMC may provide advice to Ultragenyx regarding the safety of subjects, the ethics of the study and the continuing scientific validity of the study. The DMC may also make recommendations to Ultragenyx concerning continuation, termination or other modifications of the study based on their review of data. Further details regarding the DMC will be included in the DMC charter.

The Ultragenyx Data Review Board will review the DMC recommendations and determine necessary actions that will be communicated accordingly to all stakeholders, eg, Regulatory Authorities, IRBs/IECs, and Investigators.

11.7.2. Central Independent Committee

The CIC is composed of independent GSDIa experts who are unblinded to subjects' treatment assignments. The CIC will review SMBG and CGM recordings and cornstarch use/dietary intake data on demand throughout the study to provide additional guidance to the Investigators

regarding cornstarch regimen modification. This guidance is to ensure that subjects will get the maximum benefit of their gene therapy by avoiding hyperinsulinemic responses driven by increased endogenous glucose production after DTX401 administration. The ultimate decision to reduce cornstarch intake and/or the rate of reduction will be each Investigator's responsibility, taking into account subjects' clinical status and overall safety. Additionally, the CIC will recommend an appropriate treatment regimen in response to transaminase elevations that may occur during or after the prednisolone taper. CIC will review abnormal early morning cortisol and ACTH levels obtained 24 hours after completing the prednisolone/placebo taper.

11.7.3. Role of the Independent Medical Monitor

The independent Medical Monitor will be unblinded to all data. The Medical Monitor will be privy to the treatment received for each patient to ensure that decision-making is safe for subjects (related mainly to prevention and management of hypoglycemia and management of ALT elevation related to immune reaction to AAV8).

The Medical Monitor will review all AEs and safety laboratory assessments and will communicate with the CIC and DMC as needed to provide guidance and advice to the Investigator. With regards to management of ALT elevation and immune response, the Medical Monitor will provide data summaries to the CIC to provide guidance to Investigators in situations where it might be needed to prescribe additional steroids, prolong steroids, or suggest additional laboratory tests. This also applies to the Placebo Group if ALT elevations occur. In this case, the Medical Monitor will make sure that additional laboratory tests are performed as needed while maintaining the blind for the Investigator and the subject.

The Medical Monitor will review weekly CGM reports and SMBG entries and will communicate with the Investigator. The Medical Monitor will also provide data summaries to the CIC if results warrant treatment modifications per the cornstarch management guide or any finding related to glucose values that might compromise a subject's safety.

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13. APPENDICES

APPENDIX 1. INTERNATIONAL NUTRITION GUIDANCE

The nutritional management of GSDIa is complex and based on individual patient needs. Prior to administration of the IP, DTX401 (or placebo), efforts are made to maximize the nutritional standard of care and stabilize nutritional intake. The nutritional standard of care for this Phase 3 study is based on international expert guidance (Ross et al., 2020; Kishnani et al., 2014; Froissart et al., 2011; Rake et al., 2002b; Weinstein and Wolfsdorf, 2002; Derks et al., 2021) for the treatment of GSDIa (see Study Reference Manual and Table 18). Adequate amounts of water, fiber, vitamins, and minerals to maintain the health of subjects will be determined by the Investigator and/or study dietitian trained in the nutritional management of GSDIa. During the period when subjects are treated with steroids (or placebo), the Investigator and/or study dietitian will support the subjects in limiting excessive salt and/or sodium-rich foods, as needed.

Table 18: Nutrition Guidelines for Patients Over 5 Years of Age with GSDIa

- Avoidance of fasting
- Target of 60% to 70% of total calories from complex carbohydrates, including cornstarch, distributed in small, frequent meals. Approximately 10% to 15% of total calories from protein, and the remainder of calories from fat.
- Uncooked cornstarch approximately 3 to 5 hours around the clock to provide a sustained source of blood glucose. Extended-release cornstarch (Glycosade) may be used at night to allow increased spacing of doses as tolerated. Cornstarch and Glycosade dose and frequency should be individualized, based on systematic biochemical monitoring, including trends in blood glucose, lactate, triglycerides, and uric acid.
- The nutritional regimen should target preprandial glucose above 70 mg/dL (3.9 mmol/L). Counterregulatory mechanisms engage at blood glucose concentrations below 70 mg/dL (3.9 mmol/L), with step rises in lactate levels as glucose levels decline below this threshold.
- Increased cornstarch and/or dietary complex carbohydrate doses may be needed to accommodate increased metabolic demand during puberty, increased physical activity, and acute illness.
- Limit the non-utilizable sugars fructose and galactose, including sources such as sucrose, lactose, and sorbitol.
- Avoidance of alcohol.

Source: (Ross et al., 2020; Kishnani et al., 2014; Froissart et al., 2011; Rake et al., 2002b; Weinstein and Wolfsdorf, 2002; Derks et al., 2021)

APPENDIX 2. LABORATORY ASSESSMENTS

Table 19: Specified Laboratory Assessments

Category	Assessments	Timing (Laboratory Facility Type)
Clinical chemistry panel	ALT, AST, ALP, GGT, LDH Albumin, total protein Bilirubin (total, direct, and indirect) BUN, creatinine Lipid (triglycerides, LDL, HDL, total cholesterol) panel (fasting not required) Sodium, potassium, chloride, carbon dioxide Glucose Calcium Phosphate Magnesium Creatine kinase Uric acid	At standard study visits: as specified in the Schedule of Events (Central and/or Local Laboratory[a]) On days of IP administration: approximately 0.5 and 2 hours after the start of the IP infusion (Local Laboratory)
Additional clinical chemistries	Lactate	Lactate is collected at Weeks 4, 6, and 12 in Year 1 and Weeks 52, 54, and 60 in Year 2 as well as at the discretion of the Investigator (Local Laboratory).
	Cortisol	Cortisol is collected at Week 35 and 47 (Central Laboratory[a])
	Cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, lactate, alanine, ketones STAT glucose and lactate	During the CFC (Section 10.2.4) (Local Laboratory; in regions where IGFBP1 is not available, this test is optional)
Hematology	CBC with differential	As specified in the Schedule of Events (Central and Local Laboratory[a])
Coagulation panel	PT/INR aPTT	As specified in the Schedule of Events (Central and Local Laboratory[a])
Urinalysis	Specific gravity, pH, glucose, protein Blood and ketones Microscopic examination (if blood or protein is found)	As specified in the Schedule of Events (Central and Local Laboratory[a])
Virus screening	HIV HBV HCV	Screening (central laboratory)

Category	Assessments	Timing (Laboratory Facility Type)
Other	24-hour total urine collection (Section 10.4.8)	Prior to each CFC as specified in Schedule of Events (Section 10.2.4)
	AAV8 TAb assay (Section 10.5.1)	As specified in the Schedule of Events (Specialty Laboratory)
	ELISpot assay (Section 10.5.2)	As specified in the Schedule of Events (Specialty Laboratory)
	Anti-AAV8 IgG assay (Section 10.5.3)	As specified in the Schedule of Events (Specialty Laboratory)
	Anti-G6Pase antibody assay (Section 10.5.4)	As specified in the Schedule of Events (Specialty Laboratory)
	Complement activity (C3, C4, SC5b-9, CH50, AH50, MBL; Section 10.5.5)	As specified in the Schedule of Events
	Serum pregnancy test (Section 10.4.9)	Screening and as specified in the Schedule of Events (Central Laboratory[a])
	Urine pregnancy test (Section 10.4.9)	As specified in the Schedule of Events (Local Laboratory)
	9-panel urine drug screen	Two time points at least 4 weeks apart prior to dosing in Year 1 (Central Laboratory)

[a] Samples will be sent to the central laboratory unless results are needed for clinical decision purposes. For example, standard clinical chemistry analyses should be performed locally on the day of/day after IP administration to inform hospital or research facility discharge timing. Blood collection may be performed at care visits arranged by the study site or at the study site, according to local medical practice and/or subject preference.

AAV8, adeno-associated virus serotype 8; ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CBC, complete blood count; CFC, controlled fasting challenge; G6Pase, glucose-6-phosphatase (protein); GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high density lipoprotein; HIV, human immunodeficiency virus; IGFBP1, insulin like growth factor binding protein 1; INR, international normalized ratio; IP, investigational product; LDH, lactate dehydrogenase; LDL, low density lipoprotein; PT, prothrombin time; STAT, as quickly as possible; TAb, total antibody (assay)

APPENDIX 3. CONTRACEPTION GUIDANCE

The guidance below applies for development products with potential or unknown reproductive toxicity (for products in clinical trials, where preclinical data are indicative of risk or have not yet been completed).

Female subjects of childbearing potential who are heterosexually active must consent to use a highly effective method of contraception as listed below to prevent pregnancy over the time period required for product levels to decrease to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity. This time period is generally determined by the pharmacokinetic properties of the study product and nonclinical reproductive toxicity data and is defined in the protocol or product Investigator Brochure.

Highly effective contraceptive methods are those with a failure rate of less than 1% per year when used consistently and correctly.

Female subjects of childbearing potential are defined as having reached menarche prior to or during the study. Females not of childbearing potential include those who have not experienced menarche, are postmenopausal (defined as having no menses for at least 12 months without an alternative medical cause), or are permanently sterile due to having total hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient and multiple measurements are needed.

Male subjects who are heterosexually active with female partners of childbearing potential must consent to use one of the highly effective methods of contraception listed below to prevent pregnancy over the period defined in the protocol or product Investigator Brochure. The time period required is generally determined by the pharmacokinetic properties of the study product and nonclinical reproductive toxicity data, plus 90 days for a full sperm cycle.

Highly effective methods of contraception (CTFG, 2020) include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (eg, oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (eg, oral, injectable, implantable)
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization, also called vasectomy

- Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period associated with risk of the IP and other study treatments or procedures.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
  - Abstinence is only considered a highly effective method of contraception if practiced consistently for the entire period of exposure to IP or other study treatments.
  - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception.

Note: Barrier methods (such as a condom used with or without a spermicide or a diaphragm or cervical cap used with a spermicide) used alone are NOT highly effective contraception methods.

Additional Requirement: If IP is an advanced therapy medicinal product (eg, gene therapy), a condom with spermicide is also required to be used by all sexually active males in the study in order to prevent potential transmission of the vector via seminal fluid.

APPENDIX 4. SAFETY DEFINITIONS AND ASSESSMENTS

Adverse Event (AE) and Treatment-Emergent AE (TEAE)

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity or a change in the quality of the disease or condition. Worsening of a pre-existing condition is considered an AE.

Any abnormal laboratory test results (hematology, clinical chemistry, or urine) or other safety assessments (eg, vital sign measurements), including those that worsen from screening/baseline that are felt to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs. A TEAE is defined as any new AE or any ongoing AE that worsens after IP dose administration.

Serious Adverse Event (SAE)

An SAE is an AE that meets any of the following criteria in the view of either the Investigator or Ultragenyx:

- Death
- Life-threatening
  - A life-threatening AE is an event that places the patient or subject at immediate risk of death. It does not include events that might have caused death if they had occurred in a more serious or severe form. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.
- Inpatient hospitalization or prolongation of existing hospitalization
  - Hospitalization is defined by Ultragenyx as emergency room visit that are related to the study or study procedure, any medication used in the study (eg, DTX401, corticosteroids), or a complication from a procedure; or, a full admission to a hospital for a period of 24 hours or longer for diagnosis and treatment. This includes prolongation of an existing inpatient hospitalization. Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include the following:
    - Preplanned or elective procedures scheduled prior to study enrollment (eg, outpatient surgery)
    - Protocol procedures
  - Hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

  - AEs requiring hospitalization should be considered SAEs. Hospitalizations planned prior to study enrollment (eg, for elective surgery or routine clinical procedures) that are not the result of an AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either “serious” or “nonserious” according to seriousness criteria described above.

- Disability/incapacity
  - An AE is disabling or incapacitating if it results in substantial and/or permanent disruption of the subject’s ability to carry out normal life functions.
- Congenital anomaly/birth defect not present at screening
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the criteria listed in the definition. Examples of such events are as follows:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm or events that require other management including intravenous fluids (such as antibiotics) administered in the emergency room, clinical site or by a visiting home nurse
  - Blood dyscrasias that do not result in inpatient hospitalization
  - Development of drug dependency or drug abuse

The Sponsor will utilize the “Other Serious (Important Medical Events)” category for any SAE that results from an emergency room visit requiring medical intervention related to the study or a study procedure. For example, this would include subjects that, due to hospital capacity, could not be admitted (eg, due to COVID-19 pandemic).

Adverse Event of Special Interest (AESI)

An AESI is an AE of scientific or medical interest specific to the product (or product class) or program requiring further investigation and ongoing monitoring to better characterize them. Such events can be serious or nonserious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. All AESIs should be reported to Ultragenyx as AEs or SAEs with severity and causality as outlined in this section and Appendix 5.

Vector-induced hepatic effects are considered to be adverse events of special interest (AESIs) for this study and are defined as clinically significant increases in aminotransferase levels in the medical and scientific judgment of the Investigator following IP administration. Clinically significant increases in aminotransferase levels have been observed across various AAV gene therapy clinical studies in multiple indications.

Infusion-related reactions (IRRs) including hypersensitivity have been identified as an important potential risk and AESI for DTX401. IRRs with features of hypersensitivity have been observed with blinded IP in this trial, including anaphylaxis. IRRs for this study are defined as adverse events with features of hypersensitivity with onset during the infusion or up to 6 hours after end of the infusion.

Adrenal insufficiency is considered a potential risk of study-related procedures and is an AESI. Events of adrenal insufficiency attributed to prednisolone/placebo administration have been observed in this study.

Participation-emergent Adverse Events

These events may be related to study participation or biological specimen collection and will be reported by the Investigator and noted as related to study intervention in the CRF. These participation-emergent AEs may be related to study procedures or assessments performed, the prophylactic corticosteroid regimen, or standard -of -care medications (including tapering of standard of care and any combined effects of study drug and standard of care given together). The relationship and action taken (as needed) will be reported by the Investigator and noted as such in the CRF for these types of AEs. Additionally, the severity, duration, seriousness, any required treatment or evaluations, and outcome should also be reported.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. All cases of overdose (with or without associated AEs) will be documented in the CRF. If IP is not provided under the protocol, this paragraph does not apply.

Assessment of Severity

The severity or intensity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of all AEs will be graded using CTCAE Version 5.0 (DHHS, 2017). However, for severity assessment of abnormal clinically significant laboratory values for certain disease specific laboratory tests which may be elevated at baseline for GSDIa patients including ALT, AST, triglycerides, uric acid, lactate, and cholesterol including its fractions (eg, LDL, HDL, and total cholesterol), severity grading using the definitions below should be utilized. In addition to the specified laboratory tests listed above, if an AE cannot be graded using the CTCAE criteria, it should be graded using the following definitions:

- **Mild** (Grade 1): Participant has awareness of signs or symptoms, but they are easily tolerated and are of a minor irritant type, causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate** (Grade 2): Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe** (Grade 3): Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

- **Life-threatening** (Grade 4): Events that place the participant at immediate risk of death or are disabling.
- **Death** (Grade 5): Events that result in death.

Note: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Assessment of Causality

The Investigator will make a causality assessment about the relationship of each AE to study drug. Treatment-related conditions must be distinguished from disease-related conditions.

The Investigator should determine the causality (relation to the study drug) based on his/her clinical experience and on the information given in the DTX401 IB. The causal relationship of all AEs to the study drug will be judged as either related (which includes possibly, probably, or definitely related) or not related (which includes unlikely or doubtfully related).

To ensure the consistency of AE and SAE causality assessments, Investigators should apply the following general guidelines:

A **related** causal relationship means that there is at least a reasonable possibility that the event is caused by the study drug or the research procedures. There may be a reasonable possibility of a causal relationship between study drug/IP and the AE when the event meets the following criteria:

- The event follows a reasonable temporal sequence post IP administration.
- The event is known to be or could be a response to the IP, based on preclinical or clinical data with the product or similar products.
- The event could not be explained by the subject's primary disease, including progression/expression of the disease state, other concurrent or underlying illness, and/or prior/concomitant therapies.

Not related means there is unlikely to be a reasonable possibility of a causal relationship between the event and study drug/IP or the research procedures, and/or that there is a clear causal relationship between other conditions and the AE. There is not likely to be a reasonable possibility of a causal relationship between study drug/IP and the AE when the event meets the following criteria:

- The event does not follow a reasonable temporal sequence post IP administration.
- There are no data with the IP or similar products suggesting the event occurs or may occur with the IP.
- There is a more likely alternative etiology, such as subject’s underlying primary disease, including disease progression or expression, other concurrent or underlying illness, or prior/concomitant therapies.

Note: The Investigator's assessment of causality for individual AEs is part of the study documentation process and will be recorded in the patient's medical record, CRF, and SAE form, if applicable. AEs recorded without the Investigator's assessment of the relationship to study drug will be followed up until causality is assigned.

Suspected Unexpected Serious Adverse Reaction (SUSAR) means an SAE that occurs in a clinical trial subject and is assessed by the Investigator or Ultragenyx as being serious and unexpected based on Reference Study Information (eg, IB) and as having a reasonable possibility of a causal relationship with the study drug/IP.

Urgent Safety Measure means any measure taken to protect the subjects of a clinical trial against an immediate hazard to their health or safety.

APPENDIX 5. ADVERSE EVENT COLLECTION, ELICITING, RECORDING AND REPORTING

Table 20: Collection Period and Reporting Timeframes for Adverse Event and Other Safety Information Reporting

Event Type	Collection Period	Reporting Timeframe	Report to:
Serious adverse event (SAE)	Start: From the time the subject signs the ICF End: Up to 30 days after the End of Study Visit or Early Withdrawal/Termination 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.	Report all SAEs within 24 hours of site investigator, designee, or site personnel's knowledge of the event	**Electronic Data Capture (primary)** **Ultragenyx** ***(back-up if Electronic Data Capture is down or not available)*** email: ultragenyx@primevigilance.com Fax: +1 415 930 4033
Adverse event (AE)	Start: From the time the subject signs the ICF End: Up to 30 days after the End of Study Visit or Early Withdrawal/Termination Visit	Report all nonserious AEs within a target of 3 business days of site investigator, designee, or site personnel's knowledge of the event	**Electronic Data Capture (primary)** **Ultragenyx** ***(back-up if Electronic Data Capture is down or not available)*** email: ultragenyx@primevigilance.com Fax: +1 415 930 4033
Adverse event of special interest (AESI): Adrenal insufficiency	Start: From the time the subject signs the ICF End: Up to 30 days after the End of Study Visit or Early Withdrawal/Termination Visit	All events of adrenal insufficiency, regardless of seriousness, must be reported within 24 hours of site Investigator, designee, or site personnel's knowledge of the event	**Electronic Data Capture (primary)** **Ultragenyx** ***(back-up if Electronic Data Capture is down or not available)*** email: ultragenyx@primevigilance.com Fax: +1 415 930 4033

Event Type	Collection Period	Reporting Timeframe	Report to:
AESI: Vector-induced hepatic effects, Infusion-related reactions including hypersensitivity	Start: From the time the subject signs the ICF End: Up to 30 days after the End of Study Visit or Early Withdrawal/Termination Visit	If the AESI is serious, report within 24 hours of site Investigator, designee, or site personnel's knowledge of the event If the AESI is nonserious, report within a target of 3 business days of site investigator, designee, or site personnel's knowledge of the event	**Electronic Data Capture (primary)** **Ultragenyx** ***(back-up if Electronic Data Capture is down or not available)*** email: ultragenyx@primevigilance.com Fax: +1 415 930 4033
Pregnancy (includes partner pregnancy)	Start: From the time the subject signs the ICF End: Up to 30 days after the End of Study Visit or Early Withdrawal/Termination Visit	Report all pregnancies within 24 hours of site investigator, designee, or site personnel's knowledge of the event	**Electronic Data Capture (primary)** **Ultragenyx** ***(back-up if Electronic Data Capture is down or not available)*** email: ultragenyx@primevigilance.com Fax: +1 415 930 4033

Table 21: Safety Contact Information

Global Drug Safety & Pharmacovigilance SAE and Pregnancy Reporting	PPD 24-Hour Medical Monitor Global Hotline	Ultragenyx Medical Lead
Email: ultragenyx@primevigilance.com Fax: 1 (415) 930-4033	North America: +1 888 483 7729 EMEA and APAC: +44 122 337 4240	PPD Phone: PPD Email: PPD

APAC, Asia Pacific; EMEA, Europe, Middle East and Africa; SAE, serious adverse event

Eliciting Adverse Events

A consistent methodology of nondirective questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include the following:

"Since the last visit, has the patient experienced any health problems?"

"Have there been any new or changed health problems since you were last here?"

Recording AEs and SAEs

All AEs (ie, any new condition or worsening in severity or frequency of a pre-existing condition) experienced by the patient within the protocol -defined timeframes must be promptly documented on the CRF and SAE form, if applicable. For clinically significant worsening of a pre-existing condition from baseline, the changes will be documented as AEs on the CRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the assessment returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

For IP and for non-IP studies, any AEs or SAEs considered associated with study protocol -required procedures will also be collected.

The Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring that documentation of the events is adequate. Details of the AEs must include severity, seriousness, relationship to study drug/IP, duration (dates of onset and resolution), and outcome.

In addition, the Investigator should report any AE or SAE they are made aware of that occurs after this time period and that is believed to have a reasonable possibility of being associated with study drug.

Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF and SAE form (if applicable) rather than individual signs and symptoms. Whenever medically appropriate, the Investigator should group signs or symptoms that constitute a single diagnosis into a unifying event term. For example, record "liver failure" rather than jaundice, asterixis, and elevated transaminases, or record "upper respiratory tract infection" rather than cough, rhinitis, and sneezing. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE on the CRF and SAE form (if applicable). If a diagnosis is subsequently established, it should be reported as follow-up information by revising the CRF and SAE form (if applicable). Vague nonspecific AE terms such as "erythema," "rash," or "lump on head" should be avoided and more specific information should be provided, such as "erythematous macule on right leg," "allergic dermatitis," or "scalp cyst."

Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as the AE on the CRF and, if also serious, on the SAE form. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF.

For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the CRF.

Abnormal Laboratory Values

Only clinically significant laboratory abnormalities, in the opinion of the Investigator, are to be recorded as AEs on the CRF and SAE form (if applicable). For example, abnormalities that require study drug dose modification, discontinuation of study drug, more frequent follow-up assessments, or further diagnostic investigation may be considered clinically significant by the Investigator.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the CRF and the SAE form (if applicable).

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the CRF and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

Reporting Serious Adverse Events

Any AE that meets SAE criteria must be reported to Ultragenyx or its designee within 24 hours of the site investigator, designee, or site personnel's knowledge of the event. Regardless of causality, all SAEs must be reported during the time period specified. All SAEs must also be recorded in the patient's source documentation and on the CRF. Copies of discharge summaries, consultant reports, and any other relevant documents should be provided with the SAE report when available.

If follow-up is obtained or requested by Ultragenyx and/or the Medical Monitor, the additional information should be sent within 24 hours of knowledge.

Refer to Safety Contact Information for SAE reporting.

Reporting of Pregnancy in Subject or Partner

For protocols requiring pregnancy reporting, any reported pregnancy of a subject or a subject's partner that occurs during participation in the study will be monitored for the full duration of the study and/or followed until the outcome of the pregnancy is known. In the event of a pregnancy in the partner of a subject, the Investigator should make every effort to obtain the female partner's consent for release of protected health information.

Pregnancy in a subject or subject's partner, complications of the pregnancy, and the outcome of the pregnancy should be reported to the Ultragenyx or designee within 24 hours of site investigator, designee or site personnel's knowledge of the event.

Pregnancies will be reported by completing and submitting a Pregnancy Notification Form to Ultragenyx or designee.

Pregnancy outcomes will be reported by completing and submitting a Pregnancy Outcome Form to Ultragenyx or designee.

The following pregnancy outcomes should always be classified as serious and reported to Ultragenyx or designee within 24 hours by completing and submitting the SAE and Pregnancy Outcome Form:

- Spontaneous abortion/miscarriage
- Therapeutic abortion
- Ectopic pregnancy
- Fetal death/stillbirth
- Molar pregnancy
- Birth defect/congenital anomaly

Reporting Suspected Unexpected Serious Adverse Reactions

Ultragenyx or its designee will submit SUSARs to appropriate regulatory authorities (including competent authorities in all member states concerned), Investigational Review Boards /Independent Ethics Committees (IRBs/ECs), and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days after first knowledge of the event and follow-up information submitted within an additional 8 days. All other SUSARs will be submitted within 15 calendar days of first knowledge of the event.

The Investigator will notify the IRBs/ECs of SUSARs, in accordance with IRB/EC requirements and local laws and regulations.

Non-SUSARs will be maintained in the Ultragenyx global safety database and provided in annual safety reports and/or other aggregate periodic summary reports to regulatory authorities and IRBs/ECs per local laws and regulations.

Reporting Urgent Safety Measures

Investigators are required to report any urgent safety measures taken to protect the safety or welfare of subjects to Ultragenyx or its designee within 24 hours. Ultragenyx or its designee will inform the regulatory authorities, IRBs/ECs, and other Investigators of any events (eg, change to the safety profile of IP, major safety findings) that may occur during the clinical study that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical study, as required, in accordance with applicable laws and regulations.

The Investigator will notify the IRBs/ECs of urgent safety measures, in accordance with IRB/EC requirements and local laws and regulations.

APPENDIX 6. ETHICS AND CONDUCT

This protocol is written in accordance with the principles established by the 18th World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects and subsequent amendments and clarifications adopted by the General Assemblies (World Medical Association, 2013).

Ultragenyx and the Investigator will ensure the study described in this protocol is conducted in compliance with those principles and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), GCP, and applicable local law, eg, FDA regulations, European Union (EU) regulations, and any other local ethical and regulatory requirements ("Applicable Study Conduct Obligations"). Should a conflict arise, Ultragenyx and the Investigator will follow whichever Applicable Study Conduct Obligations afford the greater protection to the subject(s).

Institutional Review Board or Independent Ethics Committee and Competent Health Authority

The IRBs/ECs must be properly constituted boards or committees operating in accordance with Applicable Study Conduct Obligations and should safeguard the rights, safety, and well-being of all study subjects. Before screening any subject, the IRB/EC, and as applicable Competent Health Authority, must review and approve this protocol and if applicable, the associated assents and ICFs, agreed to by the study site (ie, Institution) and by Ultragenyx. Furthermore, IRB/EC and Competent Health Authority approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, unless there is a need to protect subject safety. In that case and with prior IRB/EC approval/favorable opinion, the Investigator may deviate from the protocol to eliminate an immediate hazard(s) to study subjects and will immediately notify the chair of the IRB/EC and Ultragenyx of the amendment.

If IP is provided under the protocol, IP will not be shipped to the study site until Ultragenyx or its designee has received a copy of the letter or certificate of approval/favorable opinion from the IRB/EC, all Ultragenyx-required documents, and, where required, the Competent Health Authority authorization/approval of the protocol. If IP is not provided under the protocol, this paragraph and the section on IP accountability do not apply.

Before releasing advertisements or solicitations to the public for subject enrollment in the study, such advertisements or public solicitations must be submitted to Ultragenyx or its designee for review and approval. After receiving Ultragenyx approval for the advertisements or public solicitations, the Investigator must submit them to his/her IRB/EC for review and approval before using them.

Subject Information and Consent

The contents of the ICF and any assents for minors, as well as the method of obtaining and documenting informed consent, must comply with Applicable Study Conduct Obligations.

Ultragenyx or its designee will provide the Investigator written informed consent(s), which includes assents for minors. Any revisions to the ICF must be reviewed and approved by Ultragenyx before submission to the IRB/EC for its approval. The study site agrees not to begin enrolling subjects until the IRB/EC approval is complete.

Adequate consent for access to, use of, and/or processing of coded personal health information and other personally identifiable information will be obtained in accordance with the applicable laws, such as US Health Insurance Portability and Accountability Act regulations, state data privacy laws, the EU General Data Protection Regulation, or other applicable national or local data usage and protection laws.

In accordance with applicable local laws and with the subject's express and optional consent, any remaining biological samples taken for the purposes of the study, as well as any voluntary samples, may be used by Ultragenyx for additional research and development in accordance with the subject's express consent. Any such consent will be optional and not a requirement for study participation.

Before conducting any study procedures, the Investigator must obtain written informed consent for or from each potential subject. Part of obtaining that written informed consent requires the Investigator to fully explain to each potential subject the methods, objectives, requirements, and potential risks of the study and to answer any inquiries. Furthermore, the Investigator must explain to each potential subject that the subject is completely free to refuse to enter the study or to withdraw from the study at any time without either decision impacting his/her care.
The Investigator or a qualified designee must be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction.

Pediatric subjects or adult subjects with cognitive limitations will provide written assent (if possible) and a legally authorized representative (parent or legal guardian) must provide written informed consent for such subjects. If, over the course of the study, a pediatric subject becomes old enough for a subsequent assent or reaches the legal age of majority, he/she must sign the then-age-appropriate assent or consent as the case may be.

Subjects will be given a copy of the signed ICF and/or assent and will be provided any new information during the course of the study that might affect their continued participation in the study. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF. The signed ICF or assent will remain in each subject's study file and must be available to the study monitor(s) at all times.

Data Protection, Anonymization, and Security

Any study data transferred to Ultragenyx will be coded and will not contain names or any other information that would make the subject identifiable.

Study information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Ultragenyx.

The subject must be informed that the Ultragenyx auditors or other authorized personnel appointed by Ultragenyx may examine his/her medical records. The same applies for appropriate IRB/EC members and inspectors from regulatory authorities.

Ultragenyx has a standard operating procedure to address data breaches. Ultragenyx also requires all vendors supporting the study to comply with applicable data protection laws and to agree to data protection terms that include a data breach response plan and an obligation to collaborate

with Ultragenyx. These measures exist so that Ultragenyx can mitigate the breach and meet their obligations under applicable data protection laws.

Protocol Deviations

A protocol deviation is any instance of protocol noncompliance, either at study entry or during the study conduct. A major protocol deviation is defined by Ultragenyx as a having a significant impact on clinical study efficacy data and subject rights (ICF consent), safety, or welfare. All other protocol deviations are considered minor protocol deviations.

Ultragenyx does not issue protocol deviation waivers. The Investigator must inform Ultragenyx of all protocol deviations in a timely manner, provided, however, that Ultragenyx is informed of all major protocol deviations immediately after the Investigator becomes aware of such deviations.

Future Use of Stored Study Samples

With the subject's written consent, Ultragenyx will use remaining protocol-driven samples and/or will collect optional non-protocol-required biologic samples to be used for additional future research. These samples will be de-identified and may be stored for up to 20 years from the end of the study, or shorter, as required by local law.

Additional future research (or samples to be stored) would be limited to biomarker discovery (including proteomic and lipidomic approaches, immune response and immunogenicity mitigation studies, pathophysiological studies [eg, drivers of dyslipidemia]).

Investigators and Study Administrative Structure

Prior to the Investigator beginning performance of the study, Ultragenyx must be in receipt of all essential documents, including, among others, a signed Form FDA 1572 or equivalent signed by the Investigator and any Sub-Investigators, and an appropriate Financial Disclosure Form from each.

A Coordinating Investigator will be identified for multicenter studies. The Coordinating Investigator will be selected on the basis of active participation in the study, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report.

Investigational Product Accountability

The Investigator must be thoroughly familiar with the appropriate administration and potential risks of administration of the IP, as described in this protocol and the IB, prior to initiation of the study.

IP delivered to the study site and/or Investigator must be stored in a secure limited access location at controlled temperature as described in the IB and product packaging. Any such location must be available for inspection by the study monitor or auditors for inspection at any time during the study. If subjects take IP offsite, they will be given instructions on the proper storage of IP when initially dispensed and reminded of storage requirements at all subsequent visits.

An IP accountability record must be maintained for all IP received, dispensed, returned, destroyed, and/or lost during the study. This record must be kept current and made available to

the study monitor or auditors for inspection. At the completion of the study, all unused IP must be returned to Ultragenyx and/or its designee, unless other instructions have been provided for final disposition of the IP.

Data Handling and Record Keeping

Case Report Forms and Source Documents

The Investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. Data must be recorded on CRFs, electronic or otherwise, in accordance with the Clinical Trial Agreement executed between Ultragenyx and the study site and/or Investigator. Recorded data is subject to Ultragenyx verification. All information recorded on CRFs must be consistent with the subject's source documentation. For electronic CRFs, a validated EDC system will be used for entry of the data.

Data entry and data corrections will be made only by Ultragenyx-authorized users, and will be captured in an electronic audit trail. An explanation of any data change should be recorded in the CRF. All data entered in to the CRF must be verifiable; therefore, CRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by Ultragenyx or its designee. The Investigator must allow Ultragenyx or its designee direct access to all source documents.

Data entry, data review by the Sponsor, corrections to the data by authorized users, and source data verification will occur on an ongoing basis as subjects progress through the study. Data for each subject through Day 336 will be entered, cleaned and locked before each subject is allowed to proceed to the Day 337 assessments.

Data Quality Assurance

Monitoring and auditing procedures will be implemented to ensure compliance with Applicable Study Conduct Obligations. The Ultragenyx-designated representative (ie, the site monitor) will contact the Investigator and conduct regular visits to the study site. The site monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The site monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The site monitor will maintain contact through frequent direct communications with the study site by email, telephone, facsimile, and/or mail. The Investigator and all other personnel supporting the study (ie, project personnel) must agree to cooperate fully with the site monitor and will work in good faith with the site monitor to resolve all questions raised and all identified issues.

Record Retention

For study monitoring, audit, or inspection, the IRB/EC and Ultragenyx 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.

Publication Policy

The Investigator and/or study site must submit any publication or presentation about the study to Ultragenyx prior to making it public in accordance with the process in the Clinical Trial Agreement executed between Ultragenyx and the study site and/or Investigator.

Registration of Study and Disclosure of Results

Ultragenyx will register the study and post results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations.

Budgeting and Insurance

The budget and insurance for this clinical study will be addressed in the executed Clinical Trial Agreement between Ultragenyx and the study site and/or Investigator.

APPENDIX 7. TANNER PUBERTAL STAGE SCALE

Pubic Hair Scale (Both Males and Females)

- Stage 1: No hair
- Stage 2: Downy hair
- Stage 3: Scant terminal hair
- Stage 4: Terminal hair that fills the entire triangle overlying the pubic region
- Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh

Female Breast Development Scale

- Stage 1: No glandular breast tissue palpable
- Stage 2: Breast bud palpable under the areola (first pubertal sign in females)
- Stage 3: Breast tissue palpable outside areola; no areolar development
- Stage 4: Areola elevated above the contour of the breast, forming a “double scoop” appearance
- Stage 5: Areolar mound recedes into single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion

Male External Genitalia Scale

- Stage 1: Testicular volume < 4 ml or long axis < 2.5 cm
- Stage 2: 4-8 ml (or 2.5 to 3.3 cm long), first pubertal sign in males
- Stage 3: 9-12 ml (or 3.4 to 4.0 cm long)
- Stage 4: 15-20 ml (or 4.1 to 4.5 cm long)
- Stage 5: > 20 ml (or > 4.5 cm long)

APPENDIX 8. PROTOCOL AMENDMENT HISTORY

Table 22: Protocol Amendment History

DOCUMENT HISTORY		
Document	**Date of Issue**	**Overall Rationale for the Amendment**
Amendment 2	24 Feb 2023	Clinical, operational and statistical updates
Amendment 1	08 July 2021	Clinical updates
Original Protocol	11 February 2021	Not applicable

Table 23: Summary of Changes Protocol Amendment 1 (08 July 2021)

Section # and Name	Description of Change	Brief Rationale
Schedule of Events (Table 3) Section 10.1 Data Collection Devices Provided to Subjects Section 10.2.1 Assessments of Cornstarch Therapy and Dietary Intake	The description of electronic devices provided to subjects by the study has been revised to clarify that the reason for performing self-monitored blood glucose (SMBG) will be captured in the eDiary while the results of SMBG will be uploaded to the clinical database via the internet-compatible smart device.	The operational logistics of SMBG data collection have been revised as part of the study start-up activities.
Schedule of Events (Table 3) Section 10.2.5 Glycogen Storage Disease Functional Assessment Diary	The duration of daily data collection for the Glycogen Storage Disease Functional Assessment Diary (GSD FAD) during screening has been increased from 7 to 14 days before the Baseline Visit.	These data will be used for psychometric validation of the assessments.
Schedule of Events (Table 3) Section 10.2.6 Patient Global Impression of Severity and Patient Global Impression of Change	Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) completion has been modified during screening and baseline: The PGIS will be performed twice during the Screening Period, the PGIC will be performed once during the Screening period and will not be performed at the Baseline Visit.	These data will be used for psychometric validation of the assessments.
Schedule of Events (Table 3) Section 10.2.9 Entry and Exit Interview	A subject entry interview has been added at baseline.	The entry interview will complement the subject exit interview.
Schedule of Events (Table 3) Section 10.5.1 AAV8 Total Antibody Assay	Positive samples from the AAV8 Total Antibody (TAb) assay will now be further analyzed with the AAV8 immunogenicity assay.	The additional analysis of positive samples will be used to for future DTX401-related research.

Section # and Name	Description of Change	Brief Rationale
Schedule of Events (Table 3) Section 10.5.1 AAV8 Total Antibody Assay	Clarification has been added that subjects with a positive TAb assay result at screening will not be eligible for rescreening.	A positive TAb result, which excludes subjects from study participation, is not expected to change over time.
Schedule of Events (Table 3 and Table 4)	24-hour urine collection removed from Weeks 36 and 84.	Process simplification and reduces burden on patients.
Schedule of Events (Table 3 and Table 4) Section 10.2.4 Controlled Fasting Challenge Section 10.4.8 24-Hour Urine Collection	Reference to the option for 24-hour urine collection at the clinical site before the Controlled Fasting Challenge (CFC) has been removed.	It is intended that subjects collect the 24-hour urine sample at home before the study visit. Alternative sample collection for subjects who are unable to follow protocol procedures will be addressed on a case-by-case basis by the site Investigator/staff; suggestions may be provided in a separate study manual.
Schedule of Events (Table 3 and Table 4)	Reference to the study-issued mobile phone has been changed to a study-issued computer or tablet.	Operational logistics of continuous glucose monitoring (CGM) data transfer have been updated.
Schedule of Events (Table 3 and Table 4) Section 4 List of Abbreviations and Definition of Terms Section 6 Objectives and Endpoints Section 10.2.8 Health Economics Outcomes Research Assessments	Health economics outcomes research (HEOR) assessments (medical resource utilization, work and school status and productivity) have been added to the protocol as exploratory endpoints	These assessments will support the overall benefit profile of DTX401.
Schedule of Events (Table 3 and Table 4) Section 7.1.1 Study Periods Section 7.1.5 Rationale for Study Design Section 10.5.1 AAV8 Total Antibody Assay Section 11.7.2 Central Independent Committee Section 11.7.3 Role of the Independent Medical Monitor	The review of clinical data before the Week 48 IP administration has been clarified: The unblinded Clinical Trial Manager (overseeing the pharmacy monitor) will review results from the Week 36 AAV8 TAb assay, while the Investigator will review the Week 42 assessments, to confirm that the subject is eligible to receive IP administration at Week 48.	Clarification of data review to maintain the blind.

Section # and Name	Description of Change	Brief Rationale
Schedule of Events (Table 3 and Table 4) Section 7.1.1 Study Periods Section 8.2 Exclusion Criteria Section 8.6 Screening Requirements Section 10.5.5 Other Assessments Appendix 2 Laboratory Assessments	The 8-panel urine drug screen has been revised to a 9-panel drug screen. The minimum duration of time between the 2 urine drug panel assessments during the Screening Period has been revised from 6 weeks to 4 weeks.	This is now consistent with the central laboratory standard process.
Schedule of Events (Table 3 and Table 4) Section 10.2.4 Controlled Fasting Challenge Section 10.4.7 Safety Laboratory Tests Appendix 2 Laboratory Assessments	A chemistry panel to be performed at the local laboratory has been added at baseline, before and after investigational product (IP) dosing, and at each study visit where the CFC will be performed. The schedule of events has been revised accordingly.	The local chemistry results will be reviewed before and after IP dosing and before the CFC to ensure that the subject is eligible for IP administration and to confirm clinical stability before discharge, and to support subject safety during the CFC.
Schedule of Events (Table 3 and Table 4) Section 10.3.3 Optional Blood and Urine Collection for Future Exploratory Use	The description of optional sample collection for future research has been revised to indicate that samples will be collected only from subjects who consent to this, and only if this sample would not exceed maximum blood sampling volume. The timepoints for this optional sample collection have also been revised.	Revisions were made to clarify the initial intent for subjects to consent separately to this optional sample collection, and to minimize the frequency of sample collection.
Schedule of Events (Table 3 and Table 4) Section 10.4.7 Safety Laboratory Tests	Fasting requirements have been added for blood sample collection for clinical chemistry: Samples for clinical chemistry should be collected after vital signs and other noninterventional assessments have been performed, and at least 2 to 4 hours after the subject's last meal.	This revision supports standardization of the clinical chemistry blood draw.
Schedule of Events (Table 3 and Table 4) Section 10.5.2 Cell-mediated Immune Response	Sample collection timepoints for cell-mediated immune response to G6Pase (ELISpot) have been decreased.	This change provides and optimized schedule for cell-mediated immune response based on input from Phase 1/2 study.

Section # and Name	Description of Change	Brief Rationale
Schedule of Events (Table 3 and Table 4) Section 10.5.2 Cell-mediated Immune Response	The assessment of cell-mediated immune response to AAV8 by ELISpot has been removed from the study.	Data from Phase 1/2 studies support the removal of AAV8 ELISpots.
Schedule of Events (Table 3 and Table 4) Appendix 2 Laboratory Assessments	The Day 0 and Week 48 predose hematology, coagulation panel, and urinalysis will be performed by the local laboratory instead of the central laboratory.	The results from the local laboratory will be reviewed to ensure that the subject is eligible for IP administration.
Section 4 List of Abbreviations and Definition of Terms Section 7.1.5 Rationale for Study Design Section 11.1 Sample Size Determination Section 11.3.2.1 Primary Efficacy Endpoints	The analyses of the co-primary endpoints have been changed from a generalized estimating equations (GEE) model to a mixed model repeated measures (MMRM) model, and power estimates have been adjusted accordingly.	The MMRM makes a less restrictive assumption for the missing data compared with GEE model.
Section 5.2.3 Previous Clinical Studies	The date that the first 9 subjects in Study 401GSDIA01 completed the 52-week Primary Efficacy Analysis Period (PEAP) has been corrected from January 2021 to March 2021.	This corrects an error in the original protocol.
Section 5.4 Potential Risks and Benefits Section 10.4.5 Physical Examinations	Dorsal root ganglion and peripheral nerve pathologies have been added as a potential risk with DTX401, based on reports from nonclinical studies of other rAAV gene therapy products. Subjects will be monitored for this potential risk during physical examinations and through collection of adverse event data.	This is a newly identified risk, based on available published literature.
Section 7.1.4 Number of Subjects Section 8.4.1 Subject Withdrawal	Clarification has been added that subjects who withdraw from the study after randomization will not be replaced.	Clarification of subject replacement plans.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.5 Rationale for Study Design Section 8.2 Exclusion Criteria Section 8.6 Screening Requirements Section 9.4 Restricted or Prohibited Medications, Devices, and Procedures	Details regarding positive results of a urine drug screen and the use of recreational cannabis have been added to exclusion criterion #15.	Additional detail to aid study teams.
Section 7.1.5 Rationale for Study Design Section 9.5.1 Blinding	The description of the blinding strategy has been revised in the text and in Table 6.	The presentation of blinding strategy and plans has been clarified, with no change to the original intent.
Section 7.1.5 Rationale for Study Design	Subjects who receive Placebo may now be randomly assigned to receive "sham" steroids after completing the steroid taper, in order to maintain the blind.	This change supports the study blind.
Section 8.1 Inclusion Criteria	Details regarding the definition of clinically stable glycogen storage disease type Ia (GSDIa) have been added to inclusion criterion #3.	The added details provide clarification and a more standardized definition of clinical stability.
Section 8.1 Inclusion Criteria	Inclusion criterion #4 has been expanded with examples of subject requirements, and updated to indicate that subjects will not use any CGM, or flash glucose device, or glucometer other than those supplied by the study.	This revision supports subject understanding of the study requirements to which they consent, and supports standardized data collection for the study.
Section 8.2 Exclusion Criteria	In exclusion criterion #6, the definition of non-fasting triglycerides has been detailed as it relates to timing of blood draw.	This revision standardizes the timing of triglyceride blood draw, as possible, and describe the longest fasting period.
Section 8.2 Exclusion Criteria	Reference to specific antibody/antigen results necessary for documenting hepatitis has been removed from exclusion criterion #7.	The presence or history of hepatitis infection will be determined by the site's standard process.

Section # and Name	Description of Change	Brief Rationale
Section 8.4.2 Study Discontinuation, Pausing, or Suspending Enrollment	The drug-induced liver injury (DILI) thresholds have been clarified and expanded.	The updated thresholds account for different baseline levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
Section 8.4.2 Study Discontinuation, Pausing, or Suspending Enrollment	Hepatic malignancy was removed from stopping criteria.	Hepatic malignancy can occur in GSDIa patients as part of the disease.
Section 8.4.2 Study Discontinuation, Pausing, or Suspending Enrollment	Occurrence of acute neurological event, eg, after severe hypoglycemia, has been removed from stopping criteria.	This event is already covered under another study stopping criterion.
Section 8.5 Informed Consent	The requirement for subject to consent to the disease monitoring program (DMP) at time of study consent has been removed.	Subjects will be expected to enter the DMP after completing their participation in this study, and will consent to the DMP at that time.
Section 10.2.4 Controlled Fasting Challenge	The criteria for ending the controlled fasting challenge have been updated to include when the subject experiences signs and symptoms of hypoglycemia.	This additional criterion for ending the CFC supports optimal subject safety.
Section 10.2.4 Controlled Fasting Challenge	Description added regarding an additional CGM device that may be used, at the Investigator's discretion, exclusively during CFCs.	Enhance safety of subjects participating in a CFC and protect the study blind.
Section 10.2.4 Controlled Fasting Challenge	Additional detail added to discussion of capillary glucose.	Explains specifically how the data will be used.
Section 10.4.6 Liver Ultrasound	The maximum duration of magnetic resonance imaging (MRI) image storage has been increased from 25 to 30 years.	The increase in image storage duration was made to align with the Sponsor's standard operating procedures.
Section 10.4.7 Safety Laboratory Tests	A general rule for prioritizing blood collection from pediatric subjects has been added.	This prioritization supports the collection of the most clinically significant samples (to protect subject safety and key study endpoints) while minimizing blood collection volume for pediatric subjects.

Section # and Name	Description of Change	Brief Rationale
Section 11.2 Analysis Sets through Section 11.3.2.5 Multiple Comparisons/Multiplicity Section 11.7.1 Data Monitoring Committee	The descriptions of the analysis sets and the planned methods of analysis have been revised to align with the Sponsor's standard protocol template and aligned with statistical analysis presentation in the Sponsor's other gene therapy protocols.	These revisions provide increased clarity and improved document flow.
Section 11.4 Safety Analyses	Reference to Hy's Law analysis has been removed.	This change was made to align the section with other gene therapy protocols. Specific analyses such as Hy's Law analysis will be specified in the Statistical Analysis Plan.
Section 11.5 Other Analyses	This section, formerly titled "Immune Response Analyses," has been expanded to include cell-mediated immune response, GSDIa genotyping, and COVID-19 related contingency measures.	Updated for thoroughness.
Appendix 4 Safety Definitions and Assessments	The assessment of severity has been revised to clarify that specific GSDIa-related laboratory tests will not be graded according to Common Terminology Criteria for Adverse Events (CTCAE).	For some GSDIa laboratory tests, the CTCAE criteria are not applicable.
Appendix 6 Ethics and Conduct	A list has been added for the potential uses of the clinical samples that are collected during the study and stored for future research.	The addition provides clarification regarding the limited use of stored research samples.

Table 24: Summary of Changes Protocol Amendment 2 (24 February 2023)

Section # and Name	Description of Change	Brief Rationale
Title page Statement of Compliance page	PPD is Sponsor's medical lead.	Change in personnel.
Section 5.2.3, Previous Clinical Studies	Results updated to include final data from the 401GSDIA01 Phase 1/2 Clinical Study Report (CSR) and 19 April 2022 data cut for extension Study 401GSDIA02.	Updated to include CSR final data and conclusions and latest data cut.
Section 5.4, Potential Risks and Benefits	19 April 2022 data cut indicates no DTX401-related serious adverse events (SAEs). Risks of the prophylactic corticosteroid taper regimen have been expanded. Study participants will be assessed for hypothetical risk of sensory neuropathy. Risk of infusion-related reactions, including anaphylaxis, with blinded IP added.	Add latest data cut. Provide information to sites to monitor for the known risks associated with prednisolone treatment aligned with informed consent form. Peripheral nerve pathologies have been reported in nonhuman primate studies using recombinant AAV gene therapy products. The clinical relevance is unknown and assessments have been added. Infusion-related reactions with AAV therapy have been reported.
Section 5.5, Risk Minimization	Sites must monitor subjects during and after IP administration for the signs and symptoms of an infusion reaction, including anaphylaxis, at regular time intervals prior to discharge. Resources to treat anaphylaxis must be at the bedside. Subjects and the parents/guardians will be instructed to monitor for signs and symptoms of reactions after discharge during the first 24-hour period after IP administration.	Minimization of risk to study subjects who develop infusion reactions.

Section # and Name	Description of Change	Brief Rationale
Section 6, Objectives and Endpoints	Primary endpoints updated to include only 1 primary endpoint of percentage change in cornstarch intake. Secondary efficacy endpoints subject to multiplicity updated to include percentage change in hypoglycemia as measured by SMBG and Patient Global Impression of Change. Other secondary endpoints were updated to evaluate change in time to hypoglycemia during the CFC and change in percentage glucose values in the range of 70-120 mg/dL. Tertiary endpoints were updated.	Former co-primary endpoint incorporated into secondary endpoint. Secondary endpoints updated to evaluate metabolic control in GSD1a.
Section 7.1, Study Design	Approximately 20 subjects 8 to < 18 years of age will be enrolled (increased from 10 subjects).	A few of the pediatric subjects are near adult age and Sponsor is opening opportunity for additional younger patients to participate.
Section 7.1.1, Study Periods Section 10.4.2, Severe Hypoglycemic Events Figure 1, Study Design Schematic Schedule of Events (Table 3 and Table 4)	Screening period clarified. Some screening assessments allow for retesting. Severe hypoglycemic events described and defined. Both SMBG and CGM are the primary assessment methods for glycemic stability. Detailed nutrition optimization and stabilization periods have been added and described. A holding period has been added. The Controlled Fasting Challenge (CFC) at the Week 12 and Week 60 Visits was removed and the visits were changed to outpatient visits. Liver ultrasounds were added to the follow- up schedule.	Screening period clarified to include possible extension days. SMBG and CGM data sets are being used as they are complementary; assessing glucose control with both methods provides a more complete and accurate view of glucose control. Content on nutrition optimization and stabilization has been adapted for the protocol from the Study Reference Manual so that instructions appear in both places. A Holding period has been added in unlikely event that DTX401 is temporarily unavailable. During the Week 12 and Week 60 Visits, subjects may be taking or have recently taken corticosteroids, which could confound the results of the CFC. With the removal of the Week 12 and Week 60 CFC assessments, these visits no longer need to be inpatient visits. Liver ultrasounds added for safety follow-up post dosing.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.2, Cornstarch Modification Guidance	Updated guidance to sites on CGM, SMBG, diet, and cornstarch data collection requirements (new Table 8), and modifications to nutrition plan after dosing. Added that the Investigator will be unblinded to CGM data.	Additional robust nutrition information to guide sites and ensure that subjects do not experience prolonged hypoglycemic episodes. Nutritional stability described in detail. Investigators currently modify cornstarch according to trends in CGM data. Investigators will now receive actual CGM data for review in conjunction with the unblinded Medical Monitor to facilitate safer modifications to the cornstarch regimen.
Section 7.1.5, Rationale for Study Design	Blinding Strategy includes updates for Investigator and Subject/Caregiver.	These updates provide more robust guidance on post-dose immunogenicity assessments and CGM values during CFC.
Section 7.2.1, Duration of Subject Participation	Clarified duration of subject participation with more detail on predosing period.	Provide greater clarification on subject time commitment, which may vary given individual subject blood glucose stability during predosing period.
Section 8.1, Inclusion Criteria	Inclusion Criteria (IC) #3 has been expanded with greater detail to guide sites; notably the use of SMBG and CGM. IC #4 now includes statement that subject must strictly comply with prednisolone/placebo prescription including changes in prescription that may be implemented during the study by the Investigator if needed.	More detail on cornstarch regimen to guide sites; ensure that study population is not experiencing severe hypoglycemic events before entering study with the exception of those who have experienced a transient event and recovered. Prednisolone/ placebo prescription language provides an alert to sites.
Section 8.2, Exclusion Criteria	AAV8 capsid screening requirements in Exclusion Criteria (EC) #1 have been updated. EC#3 updated for accuracy. EC#5 modified to address abnormalities that may be associated with an undiagnosed condition; also modified to guide sites on management of potential elevations in liver enzymes. Both EC #5 and #7 allow retesting if abnormal values are discovered.	Modifications for accuracy and to provide additional alerts and safety measures.

Section # and Name	Description of Change	Brief Rationale
Section 8.3, Study Continuation Criteria	A Study Continuation Criteria section was added. All subjects will be evaluated according to the Study Continuation Criteria prior to their second IP administration at Week 48. Subjects who do not meet study continuation criteria may not receive blinded IP at Week 48 but will complete the Week 48 assessments after consultation with the Medical Monitor. Additionally, the Investigator should discuss any concerns about nutritional, glycemic, or metabolic stability with the Medical Monitor before proceeding with the second IP administration at Week 48.	Additional safety measures added to ensure that subjects remain eligible to proceed with the second IP administration at Week 48.
Section 8.4.2 , Study Discontinuation, Pausing and Study Enrollment	Section updated to clarify wording on reporting of DILI and SAEs of Grade 3 and above to the DMC and regulatory authorities.	Clarification of reporting of safety events leading to study discontinuation and pausing of enrollment.
Section 9.1.4, Clinical Observation and Supportive Care	This section has been updated to describe in detail how risk minimization and subject monitoring, described in Section 5.5, will be implemented by sites. These risk minimization measures are aimed at management of potential infusion-related reactions, including anaphylaxis.	Minimization of risk to study subjects who develop infusion reactions.
Section 9.2, Prednisolone Taper	Investigators must perform additional monitoring in all subjects during the prednisolone/placebo taper regardless of whether the subject is experiencing symptoms. Prednisolone Taper Regimen is updated.	Letter signed 24 June 2022 was sent to all sites indicating new Data Monitoring Committee requirements for additional monitoring of all subjects during the prednisolone/placebo taper.
Section 9.4, Restricted or Prohibited Medications, Devices and Procedures	Guidance to sites that subjects taking beta-blocker medication should temporarily stop the medication 24-72 hours prior to IP administration.	Minimization of risk to study subjects as beta blockers may antagonize the response to epinephrine if required in the management of anaphylaxis.
Section 10.2.1, Assessments of Cornstarch Therapy and Dietary Intake	New paragraph clarifies nutritional and glycemic recordings by subjects.	Enhance safety monitoring of glycemic values.

Section # and Name	Description of Change	Brief Rationale
Section 10.2.2, Capillary Blood Glucose Monitoring	It is recommended that subjects perform SMBG at least 4 times a day. Subjects must perform SMBG at least 4 times daily for at least 4 weeks before the Baseline Visit and scheduled visits (weeks 12, 24, 30, 36, 42, 48, 60, 72, 78, 84, 90, and 96). In addition to recording SMBG results (if requested by the Investigator to support CGM readings) in the eDiary, subjects are asked to record the reason for the SMBG.	SMBG will be performed more frequently and reasons for additional SMBG measurements are to be recorded in the eDiary to enhance subject safety and ensure robust data collection.
Section 10.2.4, Controlled Fasting Challenge	Subjects will be asked to rate the severity of hypoglycemia symptoms using a questionnaire.	Ensure robust data collection and enhance the tracking and treating of subject symptoms.
Section 10.2.4.1, Laboratory Sample Collection Before, During, and After the CFC	Additional, detailed instructions on sample collection and timing for the CFC was added.	Ensure that sites have clarity on the timing of CFC sample collection.
Section 10.2.6, Patient Global Impression of Severity and Patient Global Impression of Change Schedule of Events (Table 3 and Table 4)	Assessment will be conducted less frequently.	Reduce burden on subject.
Section 10.2.7, EQ-5D-5L/EQ-5D-Y Schedule of Events (Table 3 and Table 4)	Assessment will be conducted less frequently.	Reduce burden on subject.
Section 10.3.1, Glucose-6-phosphatase Genotyping	*G6PC* mutation analysis will not be waived unless results have been obtained previously from the same laboratory conducting the analysis and are in the subject's medical records.	Ensure that *G6PC* mutation analysis is conducted or available in the subject's medical record.
Section 10.4.1, Adverse Events of Special Interest Appendix 4, Safety Definitions and Assessments	New sentence indicating that "clinically significant increases in aminotransferase levels in the medical and scientific judgment of the Investigator following IP administration" qualify as an Adverse Event of Special Interest (AESI).	The definition of an AESI has been clarified.

Section # and Name	Description of Change	Brief Rationale
Section 10.4.2, Severe Hypoglycemic Events	Severe hypoglycemic events are now described and defined in greater detail; reporting requirements are clarified.	Provide a more detailed description of severe hypoglycemic events to guide sites on safety and reporting.
Section 10.4.6, Magnetic Resonance Imaging (deleted) Schedule of Events (Table 3 and Table 4)	The Magnetic Resonance Imaging assessment for the liver has been removed.	This exploratory assessment was removed due to its unclear clinical relevance and operational challenges.
Section 10.5.3, AAV8 Binding Antibody Immunoglobulin G Assay Schedule of Events (Table 3 and Table 4)	For pediatric subjects weighing < 45kg, optional weeks are extended.	Extended optional weeks so that Investigator may use discretion based on individual subject's status and recent blood counts.
Section 11, Statistical Considerations	Primary and secondary endpoints were updated to include only 1 primary endpoint and revised secondary endpoints, this section and its subsections were updated to reflect the new statistical considerations.	New statistical analyses are required due to endpoint clarifications and some revisions.
Appendix 1, International Nutrition Guidance, (Table 18)	New Appendix 1 provides international nutrition guidance for subjects with GSDIa.	International nutrition guidance was adapted from the Study Reference Manual for the body of the protocol so that the guidelines appear in both places to ensure site staff have easy access to published guidance.
Appendix 2, Laboratory Assessments, Schedule of Events (Table 3 and Table 4)	Lactate added to laboratory assessments and is to be collected locally.	Data Monitoring Committee requires that lactate (in addition to standard chemistry and uric acid) be collected 2 weeks and 4 weeks after subject starts prednisolone/placebo.
Appendix 4, Safety Definitions and Assessments	SAE definitions updated to include events that require other management including intravenous fluids (such as antibiotics) administered in the emergency room, clinical site or by a visiting home nurse	Additional examples for important medical events were included
Appendix 5, Adverse Event Collection, Eliciting, Recording and Reporting	Ultragenyx Medical Lead updated.	Change in personnel.

STATEMENT OF COMPLIANCE

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Adeno-associated Virus Serotype 8-mediated Gene Transfer of Glucose-6-phosphatase in Patients with Glycogen Storage Disease Type Ia

Protocol Number: DTX401-CL301, Amendment 3

INVESTIGATOR SIGNATURE:

I have read the protocol and agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and all applicable regulatory requirements and guidelines.

_____

Investigator Signature Date

Printed Name: _____

SPONSOR SIGNATURE:

As the Sponsor representative, I confirm that Ultragenyx Pharmaceutical Inc. will comply with all Sponsor obligations as detailed in this protocol and in compliance with the Declaration of Helsinki, GCP, and all applicable regulation requirements and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

_____

PPD Date

PPD

Ultragenyx Pharmaceutical Inc.