



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: Jacob Bitterman, PhD
Chair of the Review Committee
Office of Therapeutic Products

Through: Brendan Day, MD, MPH
Acting Division Director, DPV, OBPV

Subject: Review of Pharmacovigilance Plan

Sponsor: Ultragenyx Pharmaceutical Inc.

Product: GENGLYCOS (pariglasgene breca-parvovec-opnr)¹

Application Type / Number BLA / STN 125858/0

Proposed Indication To reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years of age and older with glycogen storage disease type Ia (GSDIa)

Submission Date: February 20, 2026

Action Due Date: August 21, 2026

¹ Also referred to in this memo by the investigational name DTX401

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125858/0 based on the safety profile of pariglasgene breCAPARVovec. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for pariglasgene breCAPARVovec, should the indication for this product be approved. Please refer to Appendix I for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Glycogen storage disease type Ia (GSDIa), also known as von Gierke disease, is a rare and potentially life-threatening disease due to a mutation in the glucose-6-phosphatase (*G6PC*) gene, which produces glucose-6-phosphatase (G6Pase) enzyme. G6Pase is essential for glucose release during gluconeogenesis and glycogenolysis. GSDIa typically presents in infancy with hypoglycemia and metabolic abnormalities. Long-term complications include impaired growth, hepatomegaly, hepatic adenomas, hepatocellular carcinomas, nephromegaly, and renal dysfunction. It occurs in about one in 100,000 persons (Kruger et al., 2025).

Currently, no approved pharmacological therapies treat the underlying cause of GSDIa. Present therapies focus on glucose control through blood glucose monitoring, glucose replacement, and strict dietary control with the avoidance of fasting. Cornstarch therapy remains the primary treatment in patients with GSDIa because its slow digestion allows for prolonged glucose release. Pariglasgene breCAPARVovec is an adeno-associated virus (AAV) gene therapy to treat GSDIa by delivering *G6PC* to hepatocytes allowing for G6Pase production. Pariglasgene breCAPARVovec retains native human *G6PC* promoter and enhancer elements, which allows for function under the control of normal hormonal regulatory responses. Transgene expression and subsequent G6Pase activity initiates within one week of treatment and reaches maximum levels within several weeks.

3 PRODUCT INFORMATION

3.1 Product Description

Pariglasgene breCAPARVovec is comprised of a non-replicating, recombinant AAV serotype 8 (AAV8) based vector. It contains a codon-optimized, wild-type human *G6PC* gene under the control of native *G6PC* promoter and enhancer elements. Pariglasgene breCAPARVovec is produced using recombinant DNA technology in human embryonic kidney cells.

Pariglasgene breCAPARVovec is a sterile, clear and colorless suspension for intravenous infusion after dilution. Each vial contains 2 mL of pariglasgene breCAPARVovec at a concentration of 3.0×10^{13} genome copy per mL and the following excipients: polaxamer 188 (0.1 mg/mL), tris (2.4 mg/mL), sodium chloride (11.7 mg/mL),

magnesium chloride (0.2 mg/mL), and water for injection, (b) (4). The total dosing requirement is calculated in correspondence to the patient's weight.

3.2 Proposed Indication

The indication statement in the initially proposed USPI, submitted to BLA 125858/0.0 on August 8, 2025, is as follows:

(b) (4)

On August 17, 2026, the sponsor submitted a revised USPI to BLA 125858/0.57, with the following indication statement:

“GENGLYCOS is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years of age and older with glycogen storage disease type Ia (GSDIa).”

OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

There are no approvals outside of the United States for pariglasgene brecaparyovec.

5 DESCRIPTION OF DTX401 CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data was reviewed from the Summary of Clinical Safety submitted to BLA125858/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125858/0 be approved. Please refer to the package insert for the final clinical safety data.

The safety data of pariglasgene brecaparyovec (referred to as DTX401) was based on three clinical studies (401GSDIA01, 401GSDIA02, and DTX401-CL301). Study 401GSDIA01 (to be referred to as Study 1) was a phase 1/2 open-label, single-arm, multicenter study. Patients enrolled in Study 1 were followed for further safety evaluation in Study 401GSDIA02 (to be referred to as Study 2). DTX401-CL301 (referred to as Study 3) was a phase 3, randomized, double-blind, placebo-controlled study. Across all three studies, 52 patients were dosed with DTX401 (12 subjects in Studies 1 and 2 and 40 subjects in Study 3). The registrational dose of DTX401 was administered to 49 (29 males and 20 females) of these 52 subjects. The median age of

study participants receiving the registrational dose is 21.0 years. Subjects in Study 1 were divided into four cohorts, with cohort 1-2 receiving reactive corticosteroids in the event of ALT elevations. Cohort 4 received prophylactic oral corticosteroids. In Study 3, all subjects receiving DTX401 completed a blinded prophylactic oral prednisolone taper regimen, initiated 14 days after blinded IP administration (Day 15 or Day 352), planned for a sustained four weeks, followed by a four-week taper. Study 3 is ongoing and as of 03 March 2025, the mean duration of exposure to DTX401 was 669 days. The total patient-years of exposure was 131.7 years for subjects in the total DTX401 group and 114.1 years for subjects in the DTX401 registrational dose group.

A summary of each study is presented in Table 1. The safety data for pariglasgene brecaaparvovec were based primarily on results of Study 3.

Table 1. Summary of clinical studies supporting the safety of Pariglasgene brecaaparvovec

Study ID	Study Design and Description	Patient Demographics	Safety Endpoints
401GSDIA01 (Study 1)	Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study; Participants received a single dose of 2.0×10^{12} GC/kg (n=3) or 6.0×10^{12} GC/kg (n=9 receiving registrational dose) as measured by qPCR; 52 weeks of follow-up	≥ 18 years old with confirmed diagnosis of GSDIa; n =12	Collection of AEs, hypoglycemic events, laboratory data, vital signs, physical examination, liver ultrasound and magnetic resonance imaging (MRI), electrocardiograms (ECG), vector determination in blood and vector shedding, immunogenicity
401GSDIA02 (Study 2)	Phase 1/2, long-term follow-up study to evaluate safety and efficacy; Participants received DTX401 in Study 401GSDIA01 (no additional dosing); mean follow-up post-DTX401 administration was 4.9 years.	≥ 18 years old with confirmed diagnosis of GSDIa; n =12	Collection of AEs, laboratory data, vital signs, physical examination, liver ultrasound and MRI, ECG, vector determination in blood
DTX401-CL301 (Study 3)	Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study;	≥ 8 years old with confirmed diagnosis of GSDIa; n = 49,	Collection of AEs, laboratory data, vital signs, physical

	Single dose of 1.0×10^{13} GC/kg as measured by ddPCR (equivalent to 6.0×10^{12} GC/kg dose by qPCR) with 40 additional subjects receiving registrational dose	including 15 pediatric subjects	examination, liver ultrasound, ECG
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*Adapted from Table 1, Summary of Clinical Safety, STN 125858/0, Module 2.7.4

5.2 Adverse events

The safety measures included treatment-emergent adverse events (TEAEs) and serious TEAEs, and death. At the time of data analysis, important identified risks for DTX401 included infusion-related reactions (IRRs) and hepatic reactions. Based on known class effects of AAV-mediated gene therapies, important potential risks for DTX401 included insertional mutagenesis and malignancy, thrombotic microangiopathy (TMA), and dorsal root ganglion (DRG) and peripheral nerve effects. Potential risks for DTX401 include hypertriglyceridemia. Potential risks of study-related procedures associated with corticosteroid administration include adrenal insufficiency. Safety data is available for 52 subjects dosed with DTX401 (referred to as the Total DTX401 group), including 49 subjects that received the registrational dose. The following study results refer to the pooled data of the 49 subjects that received the registrational dose, unless otherwise specified. Per the sponsor assessment, the results of the total DTX401 group were largely consistent with results in the DTX401 Registrational Dose group.

5.2.1 Integrated Data (Studies 401GSDIA01, 401GSDIA02, and DTX401-CL301)

5.2.1.1 Study results: TEAE's

All 49 patients in the DTX401 Dose Registration Group experienced at least one TEAE. Forty subjects (81.6%) had at least one TEAE that was considered related to DTX401 by the Investigator. Twenty-six subjects (53.1%) experienced at least one serious TEAE, with five subjects experiencing serious TEAEs considered related to DTX401 by the Investigator.

The most frequently reported TEAEs were from the System Organ Class (SOC) Investigations (n = 184), Infections and infestations (n=155), Metabolism and nutrition disorders (n=165), and Gastrointestinal disorders (n=89).

Nearly 90% of subjects (n=44/49) experienced a TEAE in the Investigations SOC, with most referring to transaminase elevations. The preferred terms (PTs) transaminases increased (29/49 subjects), ALT increased (16/49 subjects), and Gamma-glutamyl transferase increased (15/49 subjects) were most frequent. Most events were nonserious (98.9%; 182/184), mild to moderate in severity, transient, asymptomatic, and managed with reactive or prophylactic steroids.

Forty subjects (81.6%) experienced a TEAE in the Infections and infestations SOC, with the most frequent PTs of upper respiratory tract infection (17/49 subjects), coronavirus disease 2019 (COVID-19) (14/49 subjects), gastroenteritis viral (12/49 subjects), and nasopharyngitis (11/49 subjects). Most events were nonserious (87.1%; 135/155), except for those associated with gastroenteritis.

In the Metabolism and nutrition disorders SOC, the most frequent PTs were hypertriglyceridemia (16/49 subjects), hypoglycemia (14/49 subjects), and hyperglycemia (11/49 subjects). The majority (89.1%; 147/165) of events were nonserious.

More than half of subjects (57.1%) experienced a TEAE in the Gastrointestinal disorders SOC, with the most frequent PTs being nausea (14/49 subjects), diarrhea (10/49 subjects), and vomiting (9/49 subjects). Most events were nonserious (98.9%; 88/89), mild to moderate in severity, and assessed as unrelated by the Investigator.

Relatedness of AEs to corticosteroid use was evaluated during Study 3. Among the DTX401 group (Day 1 + Week 48) from Study 3, 75% of subjects experienced at least one TEAE considered related to prednisolone. Most events were nonserious, mild to moderate in severity, occurred during the prophylactic immunomodulatory corticosteroid taper regimen per protocol, and were consistent with prednisolone adverse reactions. Risk minimization measures were implemented to increase monitoring during steroid treatment with no subsequent reported serious TEAEs of adrenal insufficiency.

Reviewer comment: Hepatic reactions, evidenced by elevated transaminases and associated laboratory findings, are known risks among the class of AAV-mediated gene therapies. Reported events during clinical trials were mainly nonserious, mild to moderate severity, transient, asymptomatic, and managed with steroids. There were no events of acute liver failure or death associated with liver failure. However, given the known class effects of hepatotoxicity for AAV gene therapies, it is possible that serious and/or fatal hepatotoxicity events could occur in the postmarketing setting once the product is used in a larger and more diverse patient population. The events of hypertriglyceridemia, hypoglycemia, and hyperglycemia are likely confounded by indication given they are commonly observed findings in patients with GSDIa. Additionally, gastrointestinal symptoms such as diarrhea are common side effects of cornstarch treatment, the current standard therapy for patients with GSDIa. Risk minimization measures were implemented in response to the two serious events of adrenal insufficiency, requiring increased monitoring during steroid treatment. No subsequent serious TEAEs of adrenal insufficiency occurred following implementation of risk mitigations.

5.2.1.2 Serious Adverse Events

In the DTX401 Registrational Dose group, 26 subjects (53.1%) experienced at least one serious TEAE. The most common serious TEAEs included gastroenteritis viral (n=6), gastroenteritis (n=5), lactic acidosis (n=5), and hypertriglyceridemia (n=4). Five subjects experienced five serious TEAEs considered by the Investigator to be related to DTX401. These included anaphylactic reaction (n=2), hypertriglyceridemia (n=2), and

hyperlactacidemia (n=1). There was one serious event of lactic acidosis considered related to corticosteroid administration by the Investigator. One subject experienced a life-threatening serious TEAE of multiple organ dysfunction syndrome (due to septic shock from cholecystitis 3 years after DTX401 administration) that was not considered related to DTX401 or corticosteroids. All serious events resolved or resolved with sequelae. Please see the clinical memorandum for FDA's clinical review and assessment of safety data. Please see the appendix for detailed case narratives of the serious TEAEs considered by the Investigator to be related to DTX401.

5.2.1.3 Withdrawals Due to AEs

Across all studies, no subjects who received DTX401 discontinued the study due to a TEAE. Two subjects experienced anaphylactic reactions during the administration of DTX401 during Study 3, resulting in immediate discontinuation of the infusion for both subjects. One of these subjects was subsequently withdrawn from the study by their family after completion of the primary efficacy analysis period.

5.2.1.4 Deaths

There were no deaths reported in any patient that received DTX401.

5.2.1.5 Adverse Events of Special Interest (AESI): Important identified and important potential risks of DTX401

The sponsor describes TEAEs for the important identified and important potential risks. For the important identified risk of IRR, there were two serious events under the PT anaphylactic reaction that resulted in immediate discontinuation of the infusion. For the important identified risk of hepatic reactions, 77.6% of subjects (n=38/49) experienced at least one TEAE of hepatic reactions; except for one serious event of transaminases increased, events were nonserious, transient, and resolved or improved with corticosteroid treatment.

Reviewer comment: The one serious event of transaminases increased occurred in a subject in the crossover group who had received placebo but was never administered DTX401 due to the worsening transaminases.

For the AAV-related important potential risks of insertional mutagenesis and malignancy, TMA, and DRG and peripheral nerve effects, there were no events reported indicative of AAV8-related effects per the sponsor.

Reviewer comment: There were no events suggestive of AAV-related insertional mutagenesis and malignancy. However, the clinical trial safety database was limited in size, and given the potential risk of tumorigenicity of AAV vectors, it is possible that secondary malignancy cases could emerge in the postmarket setting once the product is used in a larger patient population over a longer duration of time. There was one subject (Subject (b) (6)), a 39-year-old male with a PMH of basal cell carcinoma (BCC), that experienced a BCC with onset more than four years after DTX401 administration. The subject with BCC had a history of BCC prior to DTX401 administration, which is more likely related to his recurrence of BCC four years after DTX401 administration.

Three hepatic adenomas were reported in Study 3 – one in the placebo group, one in the DTX401 group, and one in the crossover placebo to DTX401 group. All were nonserious, mild to moderate and assessed as not related by the Investigator. Hepatic adenomas are a frequent complication in patients with GSDIa and therefore confounded by underlying disease.

For the important potential risk of DRG and peripheral nerve effects, there were four subjects in the DTX401 Registrational Dose group with four nonserious, mild TEAEs all assessed as not related by the Investigator. These included one event of hypoesthesia about six months post-DTX401 administration, one event of sensory disturbance greater than five years after DTX401 administration, one event of balance disorder 15 days after DTX401 administration, and one event of peripheral neuropathy approximately 30 days after DTX401 administration. In the Total DTX401 group, one additional subject experienced two events of hypoesthesia, both of which were nonserious, mild to moderate in severity, with onset greater than five years post-administration with DTX401. Events were confounded by GSDIa-related neuropathy, concomitant corticosteroid administration or prior medical history of sciatica.

For the important potential risk of hypertriglyceridemia, 23 subjects (46.9%) experienced TEAEs relating to hypertriglyceridemia in the Registrational Dose Group. Four subjects experienced moderate (n=1) to severe (n=2) or life-threatening (n=1) events requiring hospitalization for monitoring and cornstarch adjustments. There were no events of secondary pancreatitis or clinical sequelae of atherosclerotic disease.

Reviewer comment: Hypertriglyceridemia is a common and known complication of GSDIa, and glycemic and metabolic monitoring are standard care in patients with GSDIa. Narratives of the four subjects requiring hospitalization were reviewed. Confounders, including history of hyperlipidemia and associated complications, underlying GSDIa, viral infection, and poor balance of cornstarch or carbohydrate intake were present in all four events.

For the important potential risk of adrenal insufficiency, seven subjects from the Registrational Dose Group (14.3%) experienced 10 TEAEs, all of which occurred during the immunomodulatory regimen. Two subjects experienced serious events, which met protocol-defined study pause criteria. As a result, risk minimization measures were instituted. Following addition of the risk minimization measures, one subject experienced two nonserious events of HPA axis suppression without any clinical signs of adrenal insufficiency. No additional serious events of adrenal insufficiency were reported.

Reviewer comment: Adrenal insufficiency is potential risk in the setting of prolonged corticosteroid administration. In response to two serious events of adrenal insufficiency, risk minimization measures were implemented, including increased monitoring during steroid tapering for signs or symptoms of Cushing's syndrome and adrenal insufficiency, endocrinology consultation and stress dose steroids if adrenal insufficiency is

suspected, and early morning cortisol and adrenocorticotrophic hormone testing 24 hours corticosteroid taper. No subsequent events of adrenal insufficiency were reported.

5.2.1.6 Safety Related to Immune Response to AAV8 and G6Pase

Per the Sponsor's assessment, baseline antibodies to G6Pase or the development of anti-AAV8 antibodies post-DTX401 administration had no apparent impact on the safety of subjects treated with DTX401.

5.2.1.7 Safety in Pregnancy and Lactating Females

DTX401 has not been studied in pregnant or lactating women. Pregnant mice administered DTX401 on gestation day 6 showed no adverse maternal effects or fetal abnormalities. Vector DNA was detected in the blood and placenta of pregnant mice, but not in the fetal livers. Pregnant females were excluded from all clinical trial studies. There is no data on the presence of DTX401 in human milk nor its effects on milk production or on breastfed infants.

Reviewer comment: Safety in pregnancy and lactating females remains unknown.

5.2.1.8 Safety in Pediatrics

Severe and serious TEAEs were reported more frequently in pediatric subjects, with a higher proportion of pediatric subjects (80%) experiencing serious TEAEs, as compared to adult subjects (36%). Similarly, 73.3% of pediatric subjects (n=11) experienced severe events as compared to 56.0% of adults (n=14). The Total DTX401 group included 15 pediatric patients. The most frequently reported serious events were gastroenteritis and associated gastrointestinal complaints, including gastroenteritis viral and gastritis viral. The two serious events of both IRRs and adrenal insufficiency occurred in pediatric subjects. In both instances, this led to protocol changes for risk minimization. In Study 3, three serious TEAEs of hypertriglyceridemia were reported all in pediatric subjects.

Reviewer comment: Pediatric patients did experience more severe and serious TEAEs, including two events of anaphylaxis and two events of adrenal insufficiency that led to study pauses. With only 15 pediatric patients enrolled, there is still limited data concerning the safety in pediatrics. Currently, there is no data to assess safety in pediatric patients less than eight years of age. Despite the increased proportion of reported events among pediatric subjects, children with GSDIa tend to have high morbidity and without strict nutritional management are at risk of death secondary to underlying disease. Children and adolescents may be more vulnerable to hypertriglyceridemia given changing metabolic needs with growth. There were no pediatric deaths in the study and the implemented risk minimization measures promoted improved safety among pediatric patients. Safety in pediatrics will be further studied in the postmarket setting through the sponsor's proposed GSDIa DMP.

6 SPONSOR'S PHARMACOVIGILANCE PLAN

A summary of the sponsor's pharmacovigilance plan (PVP) is provided in the table below. The sponsor will perform routine pharmacovigilance for all adverse events per the requirements of 21 CFR 600.80.

Table 2. Summary of Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified	Infusion-related reactions	Routine pharmacovigilance, Routine risk communication in the USPI (2.2, 2.4, 5.1, 6.1, 17); Risk minimization measures including premedication and slower starting infusion rate with gradual increasing rates; GSDIa Disease Monitoring Program (DMP) DTX401-CL401
Important Identified	Hepatic reactions	Routine pharmacovigilance, Routine risk communication in the USPI (2.1, 2.4, 5.2, 6.1, 8.6, 17); Risk minimization measures including patient screening of liver health and ability to receive corticosteroids/immunomodulatory therapy prior to DTX401 dosing, prophylactic oral corticosteroids, recommendation for transaminase monitoring for 6 months post-DTX401 administration, GSDIa DMP DTX401-CL401
Important Potential	Insertional mutagenesis and malignancy	Enhanced pharmacovigilance, Routine risk communication (USPI 5.3, 17), routine risk minimization including recommendation to monitor for hepatic adenoma with annual liver imaging, GSDIa DMP DTX401-CL401
Important Potential	Thrombotic microangiopathy (TMA)	Routine pharmacovigilance and GSDIa DMP DTX401-CL401
Important Potential	Dorsal root ganglion (DRG) and peripheral nerve effects	Routine pharmacovigilance and GSDIa DMP DTX401-CL401
Important Potential	Clinical consequences of hypertriglyceridemia	Routine pharmacovigilance, routine risk communication in USPI (2.7, 17), routine risk minimization including recommendation to monitor nutritional intake, glycemic

		control, and metabolic control (including triglycerides) post-administration with DTX401, and GSDIa DMP DTX401-CL401
Important Potential Risk Associated with Corticosteroid Use	Adrenal insufficiency	Routine pharmacovigilance, routine risk communication in USPI (2.1, 2.4), routine risk minimization including appropriate corticosteroid prescribing information including monitoring, duration of use, and tapering.
Missing	Long-term safety (>6 years)	Routine pharmacovigilance
Missing	Use in pregnant or lactating women post DTX401 administration	Routine pharmacovigilance, routine risk communication in USPI (8.1, 8.2), routine risk minimization including recommendation that DTX401 should not be used during pregnancy and to consider the development and health benefits of breastfeeding along with the mother's clinical need for DTX401 and any potential adverse effects on the breastfed infant from DTX401 or from the underlying maternal condition.

*Adapted from Tables 1, 2, 3, Pharmacovigilance Plan, STN 125858/0.0, Module 1.16.1

6.1 Enhanced Pharmacovigilance

The sponsor will perform expedited reporting to FAERS regardless of seriousness or label status for any malignancy and include summaries of both interval and cumulative data concerning malignancy in the periodic safety reports safety assessments for three-years post-approval.

Reviewer comment: FDA requested the above enhanced pharmacovigilance activities to obtain further characterization of the Important Potential Risk of insertional mutagenesis and malignancy in the postmarket period. The Sponsor agreed to these requests in the IR response submitted to STN 125858/0.31.

6.2 Safety-related Post-marketing Commitment (PMC) Study

The sponsor proposes a post-marketing long-term follow-up study (LTFU) and has agreed to conduct it as a PMC, to evaluate long-term safety, adverse events of special interest, and safety in pregnancy.

6.2.1 GSDIa Disease Monitoring Program: DTX401-CL401

The GSDIa Disease Monitoring Program (DMP) is a prospective, multicenter, longitudinal, observational study to evaluate the long-term safety and efficacy of DTX401 for at least ten years after administration. The DMP will enroll commercially treated adult and pediatric patients with GSDIa in the postmarket setting and will offer enrollment to all subjects in ongoing clinical studies.

Primary Objective: To evaluate the efficacy of pariglasgene brecaparvovec in patients with GSDIa

Secondary Objective: To evaluate the safety and pregnancy outcomes of pariglasgene brecaparvovec in patients with GSDIa

Study duration: Patients will be followed for at least 10 years after DTX401 administration. Total duration of the study is defined as the date of the last protocol-specified visit for assessment for the last patient in the DMP.

Inclusion criteria: Eligible individuals must meet all the following criteria:

1. Confirmed diagnosis of GSDIa
2. Patient who had DTX401 (full or partial dose) administered in a parent clinical study or prescribed DTX401 (full or partial dose) administered in a post-marketing setting.
3. Patient is willing and able to provide informed consent after the nature of the study has been explained, and prior to any research-related assessments or procedures. A legally authorized representative may provide informed consent for minors or adults with cognitive limitations.
4. Patient is willing and able to comply with all protocol requirements, including study visits, assessments, study procedures, and nutritional adjustments.

Exclusion criteria: Individuals with the presence of any condition that would interfere with study participation, interpretation of results, or affect patient's safety in the opinion of the Investigator.

Sample size: Approximately 110 patients (40 patients from the parent DTX401 clinical trials, 50 patients who receive DTX401 in the postmarket setting, and 20 patients who would otherwise be eligible for treatment with DTX401 but who have positive anti-AAV8 antibodies to serve as a control arm)

Data collection: Data will be collected across 20 sites through clinical visits, continuous glucose monitoring, laboratory studies, and liver imaging. Study assessments can be performed via telemedicine, at satellite sites, or with patient's local physician. Alternative methods of providing continuity of care may be implemented by the Investigator, including phone call visits, virtual contacts, local physician visits, or visits by mobile site staff.

Safety endpoints:

- Incidence and severity of SAEs assessed as related to pariglasgene brecaparvovec by the Investigator
- Incidence, relationship, severity, and seriousness of AESIs:
 - Important Risks for pariglasgene brecaparvovec: serious IRR including hypersensitivity, hepatic reactions (increased aminotransferase levels), and clinical consequences of hypertriglyceridemia.
 - Important risks associated with other AAV gene therapy class effects: malignancy (new or worsening of pre-existing malignancies), TMA, DRG and peripheral nerve effects, and any new potential risks of AAV therapies identified over time)
- Incidence and severity of SAEs assessed by Investigator as related to concomitant immunomodulatory therapies (corticosteroids) including adrenal insufficiency and iatrogenic Cushing's syndrome
- Incidence and outcomes of pregnancy in patients treated with pariglasgene brecaparvovec or patient's partner.

Reporting of Pregnancy in Subject or Partner: Any reported pregnancy of a subject or a subject's partner that occurs during study participation 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 outcomes of pregnancy should be reported to Ultragenyx or designee within 24 hours of site Investigator, designees, or site personnel's knowledge of the event. Spontaneous abortion/miscarriage, therapeutic abortion, ectopic pregnancy, fetal death/still birth, molar pregnancy, birth defect/congenital anomaly should be classified as serious and reported within 24 hours.

Data Analysis: Analyses will be descriptive, stratified by group (parent interventional study group as group 1 and patients prescribed in the postmarket setting as group 2), and by visit where applicable. Continuous variables will be summarized by number of patients, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized by number and percentage of patients. Change from baseline will be calculated for each post-baseline data collection point. All tabular summaries will be accompanied by individual patient listings. Baseline data from the parent studies that were collected prior to the patients' enrollment in the DMP will be linked to the DMP database.

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence and severity of all SAEs related to DTX401 will be reported by System Organ Class and Preferred Term. The incidence, relationship, severity, and seriousness of AESIs for AAV therapies will be provided. For group 2, the incidence and severity of IRRs will be provided. Events that represent SAEs assessed by the Investigator as related to concomitant immunomodulatory therapies will be summarized. Incidence and outcomes of pregnancies in patients treated with DTX401 or patient's partner will be summarized. Vital signs and physical examination findings will be

summarized. Analyses will be performed approximately annually over the course of the DMP or upon request from Health Authorities or per regulatory reporting requirements.

Study Milestones (as detailed in the sponsor's Cover Letter dated 17 August 2026, submitted to BLA 125858/0.58) are as follows:

- Draft protocol submission: October 31, 2026
- Final protocol submission: December 31, 2026
- Interim study report submission #1: August 31, 2028
- Interim study report submission #2: August 31, 2030
- Interim study report submission #3: August 31, 2032
- Interim study report submission #4: August 31, 2034
- Interim study report submission #5: August 31, 2036
- Interim study report submission #6: August 31, 2038
- Study Completion: November 30, 2038
- Final study report submission: August 31, 2039

Reviewer comment: The sponsor submitted the original protocol for the DMP (dated 14 December 2023) to BLA 125858/0.0 on August 8, 2025, as a voluntary study to evaluate the efficacy and safety of DTX401 in the postmarket setting. During review of the BLA, the review team determined that a confirmatory PMR study would be required for Accelerated Approval and that a PMC to evaluate long-term safety and risk of malignancy would be requested. The rationale for requesting the PMC included 1) the limited sample size and long-term follow up safety data for DTX401, 2) the recent approval of another AAV gene therapy product with a PMC to evaluate the risk of malignancy — FDA approved Otarmeni (BLA 125874) on April 23, 2026, with a PMC for a prospective, longitudinal study evaluating the risk of malignancy — and 3) the recent publication of an article (Ahrens-Nicklas, et al., 2026) describing the development of a neuroepithelial tumor secondary to AAV integration in a 5-year-old boy post-administration of RGX-111, an investigational gene therapy with an AAV9 serotype vector (FDA placed RGX-111 on clinical hold after this event).

There are no currently known serious risks for the use of AAV8, which is the vector utilized by DTX401. With respect to DTX401, carcinogenicity or tumorigenicity was not formally studied. There was no evidence of malignancy among mouse studies up to three months and non-human primates up to 6 months. Additionally, there was no evidence of insertion in germ line studies in offspring of mice. Lastly, there was no assessment done on insertional site profiling, which is a technique used to map, identify, and quantify where the vector integrates into a host genome.

On July 22, 2026, FDA sent the sponsor an Information Request detailing the requirements of the Accelerated Approval confirmatory PMR study and seeking their agreement on the PMC for long-term safety. FDA also advised the sponsor that they could include patients from the PMR study in the PMC for long-term safety. The sponsor responded by email on July 23, 2026, confirming their agreement to the above and providing PMC study milestones and a revised DMP protocol synopsis (dated 23 July

2026). On July 23, 2026, DPV presented to CBER's Safety Working Group and recommended a PMC for long-term safety and to evaluate the risk of malignancy in the postmarket setting. SWG concurred with this recommendation.

On August 12, 2026, FDA sent the sponsor a PMC notification letter, including a description of the PMC study. On August 13, 2026, the sponsor responded (BLA 125858/0.54) with requests that the proposed PMC text be modified to include related SAEs and AESIs instead of all SAEs and all AEs, respectively. FDA agreed with this request in an email response sent on August 14, 2026. In this response, FDA also requested final confirmation of PMR and PMC details by August 17, 2026. After the sponsor submitted their confirmation of the requested details, FDA identified that the Study Completion Date was missing from the PMC milestones. FDA asked the sponsor to confirm the PMC details again, including the Study Completion Date, and on August 17, 2026, the sponsor provided final confirmation of the PMC study details (see Cover Letter submitted to BLA 125858/0.58). See Section 9 of this memorandum for the final agreed upon PMC details.

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

7.1.1 Important Identified Risk: Infusion-related reactions

IRR is an adverse drug reaction for DTX401. In the Total DTX401 group, two subjects experienced two serious TEAEs of anaphylactic reaction. These events prompted risk minimization measures, including slower starting infusion rate with gradual increasing rates and pre-medication with acetaminophen/paracetamol, H1 and H2 blockers, further guidance to Investigators on management of IRRs, close and continuous monitoring of subjects during and after the infusion. There were seventeen patients dosed following new risk minimization measures without additional events of IRR. The important identified risk of IRR will be monitored through routine pharmacovigilance activities and through the long-term follow-up (LTFU) GSDIa DMP. In addition, the sponsor proposes risk communication and minimization measures via the USPI (2.2, 2.4, 5.1, 6.1, 17), including premedication and slower starting infusion rate with gradual increasing rates

Reviewer comment: IRRs are a known risk of DTX401. Based on the clinical presentation and the laboratory values (absence of tryptase elevation and evidence of complement consumption) and resolution without epinephrine of the two subjects that experienced anaphylactic reactions (see narratives in 5.2.1.3), it is more likely that there were complement-mediated reactions, rather than IgE-mediated. The main mitigation strategy for complement-mediated reactions is a slow, staged infusion. The introduction of a slower starting infusion rate with gradual increasing rates and pre-medication are important risk minimization measures. It is likely that the implemented risk minimization measures have decreased the risk of repeat IRR, however given only seventeen individuals were dosed with DTX401 after the implementation of the risk minimization measures, the data remains limited to understand the full impact of the implemented

measures. The Sponsor's proposed PVP for the important identified risk of IRR is acceptable.

7.1.2 Important Identified Risk: Hepatic reactions

Hepatic reactions, including transaminase elevations, are a known risk of AAV-mediated gene therapies given clearance of the therapy by hepatocytes. Hepatic reactions were a frequent occurrence among the subjects that received DTX401 at any dosage, with 85% of subjects experiencing TEAEs of elevated transaminases. The majority of hepatic reactions observed following DTX401 administration were mild to moderate, asymptomatic, and resolved without intervention. Peak elevations of transaminases were observed between weeks four and 15 for most subjects and most returned to baseline levels or within normal within one year following DTX401 administration. Corticosteroids have been shown to effectively manage such reactions. Additionally, hepatic conditions, including hepatomegaly, steatosis, hepatic adenoma, and hepatocellular carcinoma, are known complications of GSDIa secondary to the accumulation of glycogen and other metabolites in the liver, therefore the baseline liver health of a patient is a necessary consideration prior to DTX401 administration. The important identified risk of hepatic reactions will be monitored through routine pharmacovigilance activities and through the LTFU GSDIa DMP. In addition, the sponsor proposes risk communication and minimization measures via the USPI (2.1, 2.4, 5.2, 6.1, 8.6, 17). Risk minimization measures include patient screening of liver health and suitability for treatment and the receipt of corticosteroids prior to DTX401 dosing, prophylactic oral corticosteroids, and the recommendation for transaminase monitoring for 6 months post-DTX401 administration.

Reviewer comment: The sponsor has proposed risk communication and risk minimization measures including criteria for patient selection based on evaluation of liver health and baseline transaminase levels, prophylactic corticosteroids with adjustment and tapering in the event of significant transaminase elevations, and monitoring of transaminase levels for the first six months post-administration with DTX401 or longer based on patient's clinical presentation. The proposed PVP to continue to monitor for additional events of hepatic reactions in the post-marketing period through routine surveillance and through the GSDIa DMP, along with continued risk minimization measures, is acceptable.

7.2 Important Potential Risks

7.2.1 Important Potential Risk: Insertional Mutagenesis and malignancy

GSDIa is associated with the development of hepatic adenoma, which can transform into hepatocellular carcinoma. The integration of a liver-targeting AAV vector DNA into the genome potentially carries a theoretical risk of tumorigenicity in the liver and potential insertion in other non-targeted cells. No TEAEs associated with DTX401 were suggestive of insertional mutagenesis and malignancy in clinical trials. However, given the potential AAV class effect for insertional mutagenesis and malignancy, it is appropriate to label as an important potential risk. The important potential risk of insertional mutagenesis will be monitored through enhanced pharmacovigilance activities and through the LTFU GSDIa DMP. In addition, the sponsor proposes risk

communication and minimization measures via the USPI (5.3, 17). The sponsor has implemented risk minimization measures in prescribing information including monitoring with annual liver imaging, particularly in patients with additional risk factors for hepatocellular carcinoma, as well as contacting the marketing authorization holder in the event of a malignancy. The sponsor has proposed plans for testing tumor and non-tumor tissue in the event of a malignancy.

Reviewer comment: The initial pharmacovigilance plan did not include enhanced pharmacovigilance for malignancy. An information request requesting expedited (15-day) reporting to FAERS for events of malignancy, regardless of seriousness or labeled status for three years post-approval, as well as aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of malignancies in periodic safety reports was submitted to BLA 125858/0.31. The sponsor also provided a detailed plan for the collection and testing of clinical specimens (e.g. tissue biopsy of tumor and non-tumor) for vector copy number, presence of transgene, integration site analysis, and whole genome sequencing to assess for possible insertional oncogenesis and evaluate the potential causal role of DTX401. The proposed PVP to monitor for the important potential risk of insertional mutagenesis and malignancy with risk communication, enhanced pharmacovigilance, the recommendation for annual liver imaging, and the addition of the GSDIa DMP is acceptable.

7.2.2 Important Potential Risk: Thrombotic microangiopathy (TMA)

No events of TMA were identified during the clinical trials; however, TMA is a known risk among AAV-gene therapies given the potential activation of the complement system after DTX401 administration. The important potential risk of TMA will be monitored through routine pharmacovigilance activities and through long-term follow-up (LTFU) GSDIa DMP.

Reviewer comment: The proposed PVP to monitor for the important potential risk of TMA with routine surveillance and the addition of the GSDIa DMP is acceptable.

7.2.3 Important Potential Risk: Dorsal root ganglion (DRG) and peripheral nerve effects

No events of AAV-related DRG and peripheral nerve effects were identified during the clinical trials; however, DRG is a known risk among AAV-gene therapies based on nonclinical studies. The important potential risk of DRG and peripheral nerve effects will be monitored through routine pharmacovigilance activities and through the long-term follow-up (LTFU) GSDIa DMP.

Reviewer comment: The proposed PVP to monitor for the important potential risk of DRG and peripheral nerve effects with routine surveillance and the addition of the GSDIa DMP is acceptable.

7.2.4 Important Potential Risk: Clinical Consequences of Hypertriglyceridemia

Hypertriglyceridemia is a common complication of GSDIa associated with under- and overtreatment with cornstarch, illness, or changing metabolic demands. This known complication necessitates nutritional management with appropriate and timely

cornstarch and diet adjustments in patients with GSDIa with continued monitoring of glycemic and metabolic control. In some subjects, a worsening of baseline hypertriglyceridemia occurred after DTX401 administration. The important potential risk of clinical consequences of hypertriglyceridemia will be monitored through routine pharmacovigilance and the LTFU GSDIa DMP. In addition, the sponsor proposes risk communication through the USPI (2.4, 17) and routine risk minimization including the recommendation to monitor nutritional intake, glycemic control, and metabolic control (including triglycerides) post-administration with DTX401.

Reviewer comment: The initial PVP listed hypertriglyceridemia as a potential risk. FDA requested the sponsor identify hypertriglyceridemia as an important potential risk or to provide justification as to why it would not be classified as an important potential risk. The sponsor revised hypertriglyceridemia to be an important potential risk in version 2.0 (submitted to BLA 125858/0.31) with the risk minimization activities to include risk communication, risk minimization with monitoring of nutritional intake, glycemic control and metabolic control, routine surveillance and continued monitoring through the GSDIa DMP. The proposed PVP for hypertriglyceridemia is acceptable.

7.2.5 Important potential risk associated with corticosteroid use: Adrenal insufficiency

Adrenal insufficiency is a known complication subsequent to chronic steroid use. Prior to the introduction of risk minimization measures, two subjects experienced serious events leading to protocol-defined study pause and the implementation of corticosteroid administration risk minimization measures. Following addition of the risk minimization measures, one subject experienced two nonserious events of HPA axis suppression without any clinical signs of adrenal insufficiency. No additional serious events of adrenal insufficiency were reported. The important potential risk of adrenal insufficiency will be monitored through routine pharmacovigilance, the LTFU GSDIa DMP, risk communication in USPI (2.1, 2.4), and risk minimization including appropriate corticosteroid prescribing information including monitoring, duration of use, and tapering.

Reviewer comment: The initial PVP did not include the important potential risk of adrenal insufficiency. FDA requested its inclusion in the PVP, noting the discussion of study-related procedures associated with corticosteroid use as discussed in the Summary of Clinical Safety (BLA 125858/0.0). The sponsor revised adrenal insufficiency to be an important potential risk associated with corticosteroid use in version 2.0 (submitted to BLA 125858/0.31). The risk minimization activities to include routine pharmacovigilance, risk communication in the USPI (2.1, 2.4), with recommendations including appropriate corticosteroid prescribing information including monitoring, duration of use, and tapering, and continued monitoring through the GSDIa DMP are acceptable.

7.3 Important Missing Information

7.3.1 Missing information: Long-term safety

The primary missing information is the long-term safety of DTX401, specifically beyond 6 years post-administration. Routine pharmacovigilance and the LTFU GSDIa DMP will continue to monitor for any unidentified concerns associated with DTX401 administration.

Reviewer comment: The proposed PVP for long-term safety with continued routine pharmacovigilance and the GSDIa DMP for monitoring for at least 10 years post-administration is acceptable.

7.3.2 Missing Information: Use in pregnant or lactating women post DTX401 administration

No adverse maternal effects or fetal abnormalities were identified in animal studies; however, DTX401 has not been administered to pregnant nor lactating individuals. There is no data on the presence of DTX401 in human milk nor its effects on milk production or on breastfed infants. The sponsor proposes routine pharmacovigilance, routine risk communication in USPI (8.1, 8.2), and routine risk minimization including recommendation that DTX401 should not be used during pregnancy and to consider the development and health benefits of breastfeeding along with the mother's clinical need for DTX401 and any potential adverse effects on the breastfed infant from DTX401 or from the underlying maternal condition. The GSDIa DMP protocol includes specific reporting of pregnancy in any subject or their partner to allow for pregnancy outcome monitoring.

Reviewer comment: The proposed PVP to include risk communication, corresponding risk minimization recommendations, and specific pregnancy reporting requirements in the GSDIa DMP, is acceptable.

8 DPV ASSESSMENT

Based on review of available data, the safety concerns from the Phase 1/2/3 clinical studies (401GSDIA01, 401GSDIA02, and DTX401-CL301) can be monitored through routine pharmacovigilance, enhanced pharmacovigilance for any occurrence of insertional mutagenesis and malignancy and the LTFU (10-year) postmarketing commitment GSDIa DMP. Furthermore, the risks of treatment with DTX401 will be mitigated through risk communication and risk minimization measures as recommended in the USPI. The sponsor's PVP is acceptable.

The review team has determined that no FDAAA Title IX safety PMR studies are warranted based on the available safety data. Furthermore, the sponsor does not propose a REMS. The review team agrees that a REMS is not necessary to ensure the benefits of the product outweigh the risks.

9 DPV RECOMMENDATIONS

Should DTX401 be approved for the proposed indication, the sponsor's PVP (version 2.0, dated 26 June 2026) is adequate to monitor the postmarketing safety of DTX401, including:

1. Routine pharmacovigilance, which includes AE reporting in accordance with 21 CFR 600.80
2. Enhanced pharmacovigilance for postmarketing reports of malignancy for the first three years post-approval (as agreed upon in the sponsor's IR response dated 26 June 2026, submitted to BLA 125858/0.31):
 - a. Submit expedited (15-day) reports to FAERS for events of malignancy, regardless of seriousness or labeled status
 - b. Provide aggregate assessments of reports of malignancy in periodic safety reports
3. Postmarketing commitment study GSD1a DMP (as agreed upon in the sponsor's Cover Letter dated 17 August 2026, submitted to BLA 125858/0.58): A prospective, multicenter, longitudinal, observational study to assess and characterize the long-term safety and pregnancy outcomes in a minimum of 90 patients treated with pariglasgene breCAPARVovec-opnr. The study will include at least 40 patients from parent DTX401 clinical studies and at least 50 patients treated with pariglasgene breCAPARVovec-opnr in the postmarketing setting, including patients in the PMR #1 study. All patients will be followed for a minimum of 10 years after product administration. The study will assess the incidence of serious adverse events including the risk of adrenal insufficiency and malignancy at prespecified time intervals and assessments based on a clinical protocol. In addition to annual PMC reports, interim study reports will be submitted to the BLA every 2 years and should include, at least: cumulative counts of patients enrolled and their demographics, deaths, SAEs (at least possibly related to the product), AESIs (increased liver enzymes/liver toxicity, hypertriglyceridemia, hyperlactatemia, hyperuricemia, thrombotic microangiopathy, malignancies and pregnancy outcomes); and for each SAE and malignancy, patient age and other demographics, descriptions of the event, time to onset after pariglasgene breCAPARVovec-opnr administration, diagnostic testing, diagnosis, treatment, and laboratory analysis (including insertional site testing).
 - Draft protocol submission: October 31, 2026
 - Final protocol submission: December 31, 2026
 - Interim study report submission #1: August 31, 2028
 - Interim study report submission #2: August 31, 2030
 - Interim study report submission #3: August 31, 2032
 - Interim study report submission #4: August 31, 2034
 - Interim study report submission #5: August 31, 2036
 - Interim study report submission #6: August 31, 2038
 - Study Completion: November 30, 2038
 - Final study report submission: August 31, 2039

The available safety data does not substantiate a need for a PMR or a REMS. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

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APPENDIX I

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
8/8/2025	Sponsor	STN125858/0.0	Module 1.14.12 Annotated Draft Labeling Text
8/8/2025	Sponsor	STN125858/0.0	Module 5.3.5.3 Integrated Summary of Safety
8/8/2025	Sponsor	STN125858/0.0	Module 1.16.1 Pharmacovigilance Plan
8/8/2025	Sponsor	STN125858/0.0	Module 1.16.1 DTX401-CL401 DMP Protocol Final
8/8/2025	Sponsor	STN125858/0.0	Module 2.7.4 Summary of Clinical Safety
8/8/2025	Sponsor	STN125858/0.0	Module 2.5 Clinical Overview
8/8/2025	Sponsor	STN125858/0.0	Module 2.7.4 Safety Narratives for Study 401GSDIA01
6/26/2026	Sponsor	STN125858/0.31	Information Request Response, Updated Pharmacovigilance Plan
7/07/2026	Sponsor	STN125858/0.36	Information Request Response, Updated Postmarketing Study
8/17/2026	Sponsor	STN125858/0.57	Draft Labeling Text
8/17/2026	Sponsor	STN125858/0.58	Cover Letter – Acknowledgement of FDA Postmarketing Requirement (PMR) and Commitments (PMCs) Communication Dated 17Aug2026

APPENDIX 2

Case Narratives for Serious TEAEs considered by the Investigator to be related to DTX401

The narratives for subjects that experienced Serious TEAEs as described in Section 5.2.1.2 are listed below. Reported ages refer to the age at which the study drug was administered or when the subject signed informed consent, and may not represent the age at the time of described event.

1. Subject (b) (6) : 10-year-old male with a past medical history (PMH) of hepatosplenomegaly began experiencing chest pain, vomiting, tachycardia, and urticarial rash about one minute after the initiation of the DTX401 infusion. He remained normotensive and afebrile with normal oxygen saturation. The infusion was stopped immediately, and the subject was treated with ondansetron, acetaminophen, diphenhydramine, famotidine, and normal saline. He was diagnosed with anaphylaxis. Epinephrine and methylprednisolone were considered but not administered. His rash subsided after one hour and his tachycardia resolved. Serum tryptase collected one hour and 45 minutes after symptom onset was normal. All symptoms were resolved by two hours. The infusion was not resumed.
2. Subject (b) (6) : 12-year-old male with a PMH of cerebrovascular accident, seizure, hypertriglyceridemia, hepatosplenomegaly, hypertension, and gastroesophageal reflux disease started experiencing coughing and difficulty breathing approximately six minutes into the DTX401 infusion. The infusion was

stopped immediately, the patient's oxygen saturation dropped to 80%, and he was administered inhaled albuterol, oxygen via nasal cannula, and IV diphenhydramine. His respiratory symptoms improved, and his oxygen saturation increased to 91%. He developed an erythematous reticular rash, and he was given hydrocortisone IV. Epinephrine was discussed but not administered. Thirty minutes later, his oxygen saturation was 98% and the subject was able to maintain normal oxygen saturation without supplemental oxygen. The rash resolved after two hours, and all other symptoms were improved after eight hours. Tryptase levels at 30 minutes and four hours after symptom onset were normal. Complement testing performed about 2.5 hours after the reaction demonstrated evidence of complement consumption (CH50 78% of normal, AH50 45% of normal, and MBL 32% of normal). The subject had been premedicated with cetirizine and acetaminophen 30 minutes prior to initiating the infusion.

Reviewer comment: The Sponsor assessed these events as IRR with features of hypersensitivity consistent with a complement-mediated reaction rather than IgE-mediated. It is reasonable to conclude these were likely complement-mediated IRRs given that both subjects had normal tryptase levels, one with laboratory data consistent with complement consumption, neither experienced hypotension and both resolved without epinephrine. Adjusting the infusion rate can help decrease the likelihood of complement-mediated reactions. After these two occurrences, risk minimization measures were implemented, including a reduction in the initial infusion rate.

3. Subject (b) (6) : 15-year-old female with a PMH of Guillain-Barré syndrome, gastrostomy, and headache presented at the hospital on Study Day 638 (eight months after DTX401 dosing) for glucose monitoring and lactate measurements to guide cornstarch titration. The subject was found to have triglycerides to 3765 mg/dL and diagnosed with hypertriglyceridemia. She remained asymptomatic, however she did have viral gastroenteritis six days prior with associated weight loss. After two days of dietary changes and cornstarch regimen, triglycerides decreased to 1283 mg/dL and the patient was discharged in stable condition.
4. Subject (b) (6) (Registrational Dose): 31-year-old male with a PMH of pancreatitis, hyperlipidemia, and hypertriglyceridemia, experienced hypertriglyceridemia and viral gastroenteritis requiring hospitalization on Study Day 1092. The subject's hypertriglyceridemia was ongoing upon discharge (unspecific date). On Study Day 1330, the subject was readmitted for one day due to worsening hypertriglyceridemia and received ciprofibrate and ezetimibe. Genetic testing was performed but did not reveal an additional hereditary cause for the elevated triglycerides. The subject also had an elevated lactate and ketones and reported not taking any cornstarch. The patient was restarted on cornstarch and was discharged the following day after his triglyceride levels decreased from 28.3 mmol/L to 19 mmol/L.

Reviewer comment: While both events were assessed as likely related to DTX401 by the Investigator, the Sponsor assessed both events as unlikely related to DTX401

administration. Review of the details of the events associated with these two subjects includes confounders that make the relatedness to DTX401 less likely. Regarding Subject (b) (6), the event of hypertriglyceridemia is confounded by underlying GSDIa, as well as possibly attributable to the recent viral infection with weight loss which could lead to metabolic instability. Patients with GSDIa tend to be impacted by even small dietary changes and often require hospitalization for nutritional management. Increasing the patient's cornstarch dosing and other dietary changes led to improved triglyceride levels. Regarding Subject (b) (6), the event is confounded by underlying GSDIa and prior history of medically significant hypertriglyceridemia resulting in pancreatitis. Additionally, the subject had recent changes to diet and lifestyle activities which can quickly impact metabolic control in a patient with GSDIa and there was a long latency (over 3.5 years) between this event and DTX401 administration.

5. Subject (b) (6) : 17-year-old female with a PMH of amenorrhea began tapering the prednisolone regimen per protocol presented to the hospital on Study Day 48 with Kussmaul dyspnea, moon facies, dark skin, weakness, lower extremity edema, and easy bruising suggestive of Cushing's syndrome. The patient had an elevated lactate of 12 mmol/L and was diagnosed with hyperlactacidemia. The subject was treated with IV fluids, clinically recovered, and was discharged two days later. The subject remained on the prednisolone taper per protocol at 30mg/day at discharge. The patient then continued the prednisolone taper to 20mg/day per protocol. However, the dose was decreased to 10 mg after four days, rather than five days. Six days after reducing to 10 mg (Study Day 59), the subject presented to the emergency room with suspected adrenal insufficiency given hypoglycemia and compensated metabolic/lactic acidosis. The subject was treated with 100mg hydrocortisone and IV fluids and improved clinically initially. She then experienced elevated lactate, hypotension, tachycardia, and hemodynamic instability requiring transfer to intensive care. She received IV fluids and IV bicarbonate, with limited improvement. She developed vomiting, abdominal pain, and anuria requiring high dose diuretics. She had bilateral pleural effusions. After about one week after admission, the patient was transitioned out of intensive care and to oral hydrocortisone. On Study Day 76, she was discharged, and the event of adrenal insufficiency was considered resolved.
6. Subject (b) (6) : 31-year-old male with a PMH of anemia, hyperlipidemia, nephrocalcinosis, transaminase increased, hyperuricemia, hypocitraturia, presented on Study Day 42 with headache, increased abdominal pain, and foot swelling. He was hospitalized and diagnosed with lactic acidosis, with lactate levels reaching 8.9 mmol/L. The patient had no respiratory symptoms or fever. The subject had a baseline elevated lactate level of 5.3 mmol/L one day prior to DTX401 administration and had initiated prednisolone 60 mg daily per protocol two weeks after DTX401 administration. Once hospitalized, prednisolone was tapered to 40 mg daily and the subject's lactate level trended down. His lactate level was 2.8 mmol/L upon discharge on Study Day 43. No additional treatment or medication was administered, and the event was considered resolved.

Reviewer comment: Hyperlactacidemia and lactic acidosis can be drug-induced in the absence of hypoxia or tissue ischemia, secondary to increased gluconeogenesis and increased insulin resistance (reference Smith). Lactic acidosis has been reported after high-dose steroid use. Additionally, myopathy is a labeled adverse reaction of prednisolone, and myopathy can result in lactate production. Cushing's syndrome and adrenal insufficiency are both known labeled risks/adverse reactions of prednisolone. While underlying disease or potentially a baseline elevated lactate level are confounders in these subjects, it is likely that prednisolone exposure contributed to the development of hyperlactacidemia/lactic acidosis, Cushing's syndrome, and adrenal insufficiency. The latency between DTX401 administration and the development of hyperlactacidemia on Study Day 48 or lactic acidosis on Study Day 42 makes prednisolone exposure a more likely cause than DTX401 administration in these two subjects.

7. Subject (b) (6) : 39-year-old male with a PMH including cholelithiasis, chronic kidney disease (Stage 3b), nephropathy, nephrolithiasis, splenomegaly, hepatomegaly, hyperlipidemia, hepatic adenoma, hypocitraturia, peripheral neuropathy, basal cell carcinoma (BCC), recurrent bilateral first toe sores with baseline elevated transaminase levels, presented to the emergency department (Study Day 1105) with headache and nausea. His condition rapidly deteriorated, requiring vasopressor support, antibiotics, and dextrose. He was diagnosed with multiple organ dysfunction, secondary to cholecystitis and resulting septic shock. He improved throughout his hospital course, but did experience overall worsening of his CKD to stage 4, requiring hydralazine, metoprolol and isosorbide therapy. The patient was discharged two weeks later. This subject also developed two nonserious events of a BCC approximately 4.5 years post-administration with DTX401 and sensory change in bilateral hands five years post-administration with DTX401. The BCC was excised without complication. The subject did not receive any treatment or intervention for the sensory disturbance.

Reviewer comment: Given the long latency since DTX401 administration, all the described events are unlikely to be related to DTX401. While insertional mutagenesis and malignancy are an important potential risk of all AAV-mediated gene therapies, including DTX401, the subject's prior history of BCC makes the recurrences more likely related to the subject's underlying predisposition for and prior disease with BCC than DTX401. Similarly, while peripheral nerve effects are a potential risk of DTX401, the subject's peripheral neuropathy is confounded by his prior peripheral neuropathy.