Summary Basis for Regulatory Action

Date:	August, 19, 2026
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BLA STN:	BLA 125858/0
Applicant:	Ultragenyx Pharmaceutical, Inc
Submission Receipt Date:	December 23, 2025
PDUFA *Action Due Date:	August 23, 2026
Proper Name:	pariglasgene brecaparvovec-opnr
Proprietary Name:	GENGLYCOS
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)

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends accelerated approval of this product.

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Director, Product Office

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For Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
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Table of Contents

1. Introduction 4
2. Background 5
3. Chemistry Manufacturing and Controls (CMC) 7
    a. Product Quality 7
    b. Testing Specifications 9
    c. CBER Lot Release 10
    d. Facilities Review / Inspection 10
    e. Container/Closure System 11
    f. Environmental Assessment 11
4. Nonclinical Pharmacology/Toxicology 11
5. Clinical Pharmacology 12
6. Clinical & Statistical Evaluation 13
    a. Clinical Studies (Efficacy) 13
    b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance 14
    c. Pediatrics 14
    d. Other Special Populations 15
7. Safety Evaluation and Pharmacovigilance 15
8. Labeling 17
9. Advisory Committee Meeting 17
10. Other Relevant Regulatory Issues 17

    Recommendations and Benefit/Risk Assessment 17

11. 17
    a. Recommended Regulatory Action 17
    b. Benefit/Risk Assessment 18
    c. Recommendation for Postmarketing Activities 18
12. References 20

1. Introduction

Ultragenyx Pharmaceutical, Inc. submitted Biologics License Application (BLA) 125858, seeking licensure for pariglasgene brecaparvovec-opnr with the proprietary name GENGLYCOS (code name: DTX401). GENGLYCOS is an adeno-associated virus (AAV) vector-based gene therapy 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). This document summarizes the regulatory basis for accelerated approval of GENGLYCOS.

The Applicant has provided substantial evidence of effectiveness to support the accelerated approval of GENGLYCOS based on one adequate and well-controlled clinical investigation, Study DTX401-CL301, with confirmatory evidence from a nonclinical pharmacology study in (G6PC) (b) (4) mice (b) (4)

Study DTX401-CL301 was a randomized, double-blind, placebo-controlled Phase 3 study which included a primary efficacy analysis period (PEAP; Weeks 1–48) followed by a crossover period (Weeks 48–96) where patients initially randomized to placebo received GENGLYCOS. The primary efficacy analysis population included 46 patients randomized 1:1 to receive either GENGLYCOS 1.0×10^{13} GC/kg IV once or placebo. During the study, the prescribed daily cornstarch (CS) intake was modified in both groups based on blinded evaluation of glucose values (using continuous glucose monitoring) and daily dietary intake recorded in an electronic diary.

The primary efficacy endpoint was the percent change from baseline to week 48 in total daily cornstarch (CS) intake in grams (g). There was a statistically significant mean (95% CI) difference of -30.9% (-40.8%, -20.9%) in daily CS intake (g) between the GENGLYCOS and placebo groups at week 48. The secondary efficacy endpoints included the change from baseline to week 48 in the number of daily CS doses and the percentage of glucose values in the hypoglycemic range (<70 mg/dL), averaged over a 4-week period. There was a statistically significant mean reduction in the number of daily CS doses of 1.0 dose (95% CI: 0.5,1.4) in the GENGLYCOS group compared to placebo at week 48. GENGLYCOS-treated patients experienced a 3% mean increase (SD 0.9%, 5.2%) in the percentage of glucose values in the hypoglycemic range (<70 mg/dL) compared to <1% increase in placebo-treated patients at week 48.

Overall, at Week 48, patients treated with GENGLYCOS had an approximately 31% greater reduction in total daily cornstarch intake compared with patients who received placebo and a one cornstarch dose per day greater reduction. In descriptive analyses, GENGLYCOS-treated patients had numerically higher rates of hypoglycemia (blood glucose 70-54 mg/dL), plasma lactate (10% vs 0), hyperglycemia (14% vs 0%) and plasma triglycerides (29% vs 8%), indicative of potentially suboptimal metabolic control. These results suggest that the restored liver G6Pase activity with GENGLYCOS may not have fully compensated for the reduction in cornstarch intake in all patients.

The reduction in percent of cornstarch intake is used as a surrogate efficacy endpoint, reasonably likely to predict long-term clinical benefit in this application, including improved fasting tolerance and reduced rate of life-threatening hypoglycemia. A Postmarketing Requirement (PMR), to be completed within 5 years post-approval, will

verify and describe the clinical benefit of GENGLYCOS in an adequate and well-controlled study over a 2-year follow-up period. The study will assess absolute change from baseline in the number of daily CS doses and time to hypoglycemia (TTH) (blood glucose 70 to 54 mg/dL) during a controlled fasting challenge (CFC), metabolic biomarkers (triglycerides, uric acid, and lactate), and clinician-reported assessments of overall health.

Confirmatory mechanistic evidence comes from in vivo pharmacology studies in *G6PC* (b) (4) mice. In a study in 2-week-old mice, IV administration of DTX401 (at 0.09 and 1.8× the clinical dose level) resulted in dose-dependent increases in hepatic G6Pase activity and fasting glucose levels, as well as phenotypic improvements in blood glucose, cholesterol, triglycerides, hepatomegaly and nephromegaly at the higher dose.

The safety database includes 55 patients with GSDIa (35 adults, 20 pediatric patients aged 8-17 years) exposed to the proposed commercial dose of GENGLYCOS with a maximum duration of follow up of 96 weeks. The most commonly observed adverse reactions included hypersensitivity reactions/infusion-related reactions including anaphylaxis, hepatic toxicity, adrenal insufficiency, and metabolic abnormalities (hypoglycemia, high lactate, hyperglycemia, high triglycerides). Hypertriglyceridemia was observed at a higher rate in the GENGLYCOS group compared to the placebo group at 48 weeks of follow up (29% vs 8%). The observed risks were mostly mild-moderate with serious risks involving anaphylaxis and adrenal insufficiency. The observed risks and appropriate risk mitigation strategies will be communicated through product labeling and patient labeling. Continued long-term safety follow up post-approval will include routine pharmacovigilance, and a longitudinal, observational safety study as a post-marketing commitment (PMC).

One PMC includes conducting adequate analytical and clinical validation studies to specify the use of an FDA authorized in vitro companion diagnostic device to accurately and reliably identify patients who do not have pre-existing anti-AAV8 antibodies and for whom pariglasgene brecaparvovec-opnr is indicated.

One Chemistry, Manufacturing and Control (CMC) PMC regarding re-assessment of specific lot release criteria is listed in Section 11.c of this document.

Overall, the benefit-risk assessment is favorable and supports accelerated approval.

2. Background

Glycogen Storage Disease Type Ia (GSDIa) is a serious, rare, monogenic disease caused by deficient glucose-6-phosphatase (G6Pase) activity in the liver and kidneys. The fundamental pathology involves the inability of the liver to release glucose into the circulation (from glycogen breakdown) or generate glucose (through gluconeogenesis) during times of fasting and metabolic stress such as illness, exercise, physical activity, and other activities requiring glucose for energy production. Due to the enzymatic block in the pathway of glycogen breakdown, glycogen accumulates in the liver and related metabolites (lactate, fats) rise. Affected patients experience recurrent, fasting hypoglycemia, with life-threatening complications if not treated with exogenous glucose sources (e.g., cornstarch, glucose tablets). The accumulation of glucose-6-phosphate

(G6P) drives the hallmark biochemical complications of GSDIa: lactic acidemia, hyperuricemia, hypertriglyceridemia, hepatic steatosis, and hepatocellular adenoma formation, with risk of malignant transformation. Each hypoglycemic episode further worsens this cycle by triggering counter-regulatory hormonal responses that generate additional G6P, which cannot be cleared in the absence of G6Pase, amplifying downstream metabolic derangements.

GSDIa is managed through frequent daily cornstarch intake and strict adherence to a diet that restricts the intake of simple sugars, fructose, lactose and foods containing these ingredients and through frequent meals throughout the day and at night. The introduction of uncooked cornstarch (CS) in 1984 markedly improved survival as frequent CS intake (which enables slow glucose release) throughout the day and night prevents life-threatening fasting hypoglycemia which can have life-threatening consequences if untreated including seizures, coma, and death. While cornstarch extended life, sustained metabolic dysregulation continues to drive progressive end-organ damage, and complications once rarely seen, including hepatocellular adenomas, chronic renal disease, osteoporosis, gout, and pulmonary hypertension, emerged as the dominant causes of morbidity and mortality. Clinical management also includes targeted treatment of long-term disease complications such as hyperlipidemia, hyperuricemia/gout, hepatic adenomas or carcinomas, growth abnormalities (delayed growth on children or obesity in adults), renal disease, osteoporosis, and others. There are no FDA approved pharmacological therapies specifically for treatment of GSDIa. The intake of large amounts of cornstarch daily is associated with long-term complications. These include weight gain/obesity due to the additional calories with associated consequences such as metabolic syndrome, insulin resistance, and others. In addition, the highly restrictive diet can lead to nutritional vitamin and cofactor deficiencies that can interfere with growth and development in children.

The GENGLYCOS clinical studies evaluated whether GENGLYCOS enabled a reduction or reduced dependence on exogenous glucose replacement (cornstarch) to maintain euglycemia. The Applicant used total daily cornstarch (CS) intake as the primary efficacy endpoint in the Phase 3 study, Study DTX401-CL301, to establish effectiveness. The provision of exogenous glucose in the form of high and/or frequent amounts of CS is the cornerstone of GSDIa management aiming at maintaining a euglycemic state and preventing life-threatening hypoglycemia. Reducing the daily amount and/or frequency of CS needed to achieve euglycemia and/or avoid hypoglycemic events constitutes an indirect measure of better/longer fasting tolerance without the risk of hypoglycemia. Therefore, a demonstration of a meaningful reduction in CS intake (total daily intake/number of daily doses) needed to maintain a reasonable state of euglycemia serves as a surrogate endpoint that is reasonably likely to predict clinical benefit, prolonged fasting tolerance without hypoglycemia, in GSDIa and it is an appropriate endpoint to support accelerated approval.

Table 1. *Regulatory History*

Regulatory Events / Milestones	Date
IND submission	March 21, 2018
Fast Track designation granted	May 9, 2018
Orphan Drug designation granted	September 28, 2016
Regenerative Medicine Advanced Therapy designation granted	June 25, 2019
Pre-BLA meeting	December 5, 2024
Rare Pediatric Disease designation granted	December 22, 2023
BLA 125858/0 submission	December 23, 2025
BLA filed	February 20, 2026
Mid-Cycle communication	April 21, 2026
Late-Cycle meeting	June 8, 2026
PDUFA Action Due Date	August 23, 2026

3. Chemistry Manufacturing and Controls (CMC)

Based on the review of the information provided in the initial submission and the subsequent amendments, the CMC review team concludes that the manufacturing and controls for GENGLYCOS are acceptable for commercial manufacturing under the BLA. GENGLYCOS is a non-replicating, recombinant adeno-associated virus serotype 8 (rAAV8) vector encoding a codon-optimized sequence of the human glucose-6-phosphatase-α (hG6PCco) gene. The transgene expression is driven by the native human G6PC promoter/enhancer and (b) (4) The drug product is supplied as a sterile, frozen suspension containing GENGLYCOS in tris-buffered saline with 0.01% poloxamer 188 in a (b) (4) borosilicate glass vial. The drug product is sterile and contains no preservative. It is stored at ≤ -60 °C. After product thaw, each vial contains an extractable volume of 2.0 mL

a. Product Quality

Manufacturing Summary

GENGLYCOS drug substance (DS) is manufactured by (b) (4) To manufacture GENGLYCOS drug product, the DS (b) (4) concentration of 3.0×10^{13} vector genome/mL, sterile filtered, and (b) (4) mL are filled into 8 mL borosilicate glass vials. The finished drug product vials are stored frozen at ≤-60 °C. The frozen vials are shipped to a labeling and secondary packaging facility to complete the vial labeling and packaging prior to commercial distribution.

Manufacturing Control Strategy
To ensure product safety, identity, strength, purity, and potency, the CGMP manufacturing process is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) validated lot release testing. The manufacturer accepts raw materials based on in-coming acceptance tests and verification of raw material specifications. Suppliers are qualified and audited according to established supplier qualification programs. Raw materials derived from animals and humans are appropriately qualified to ensure the absence of microbial or viral contamination.

The manufacturing process control strategy includes setting acceptable limits for process parameters and testing the in-process materials, drug substance, and drug product for microbial and viral contaminants, identity, purity, strength, and potency. (b) (4) (b) (4) drug product are controlled by lot release tests including quantitative assays that measure (b) (4) , product potency, and process- and product-related impurities. Two *in vitro* potency assays assess the mRNA expression of the G6PC transgene and the activity of the resulting enzyme. All lot release tests are validated.

Process Validation
The manufacturing process was validated through production of (b) (4) process performance qualification (PPQ) drug substance lots and three PPQ drug product lots at commercial scale. All (b) (4) batches of drug substance and (b) (4) three batches of drug product met all pre-defined PPQ acceptance criteria. Additional validation studies were also performed, including aseptic filling, (b) (4) , shipping validation, and a cumulative extractables and leachables study. Process consistency will continue to be monitored and assessed post-approval following a continued process validation plan.

Stability
The drug substance is stable for (b) (4) when stored at (b) (4) The drug product shelf-life is set at 24 months based on extrapolation from real-time stability data from commercial lots and supportive data from clinical lots. Once thawed, the drug product can be stored at room temperature for up to 24 hours, or a 2-8 °C for up to 48 hours.

Comparability
Patients in the clinical studies of GENGLYCOS mostly received product manufactured using the clinical DS and DP processes. One drug substance lot manufactured using the commercial process at the clinical manufacturing facility was used during the clinical study. All clinical drug product lots used the clinical DP manufacturing process. The commercial manufacturing process introduces several modifications, including changes to the (b) (4) The clinical and commercial manufacturing processes produce products with comparable critical quality attributes, including statistically equivalent full capsid content and potency.

Manufacturing Risks
The risk of product contamination with microbial and viral adventitious agents is minimized by i) ensuring adequate control of raw materials, especially those of biological

origin that are used in the generation of cell banks and product manufacturing; ii) testing of cell banks, cells at limit of age, production cells, (b) (4) adventitious viral agents; and iii) demonstrating robust (b) (4) process. The risk of extractables and leachables that could originate from the product manufacturing process and the container closure system was analyzed, and the analytical studies and toxicological assessments were sufficient to mitigate this risk.

PMC
One PMC was agreed upon to re-assess the acceptance criteria for two process-related impurity assays and one potency assay after (b) (4) commercial lots are manufactured.

b. Testing Specifications

Table 2. Drug Product Specifications

Quality Attribute	Test Method	Acceptance Criteria
Appearance	(b) (4)	Liquid, colorless, clear to translucent, may contain proteinaceous particulates but free from foreign matter
pH	(b) (4)	7.5 – 8.5
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Poloxamer 188	(b) (4)	(b) (4)
Genome Identity	(b) (4)	(b) (4)
Capsid Identity	(b) (4)	(b) (4) consistent with AAV8 serotype
Genome Titer	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
mRNA Expression	(b) (4)	(b) (4)
In Vitro Potency	(b) (4)	Relative Potency: (b) (4)
Capsid Purity	(b) (4)	(b) (4) Purity: (b) (4)
(b) (4)	(b) (4)	(b) (4)
Endotoxin	(b) (4)	(b) (4)
Sterility	(b) (4)	Negative

The analytical methods and their validations and/or qualifications reviewed for the GENGLYCOS drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA STN 125858/0 were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of GENGLYCOS are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 3. Manufacturing Facilities Table for pariglasgene brecaparvovec-opnr, (DTX401); GENGLYCOS

Facility: Manufacturing/ Testing activities	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
Ultragenyx Pharmaceutical Inc. 170 Middlesex Turnpike Bedford, MA 01730 *DS manufacturing, DP manufacturing, and DP packaging*	3025268614	119414797	PLI	CBER/DMPQ April 2026 VAI
Ultragenyx Pharmaceutical Inc. 150 Presidential Way Woburn, MA 01801 *DP release testing*	3023224237	118377074	PLI	CBER/DMPQ April 2026 NAI
(b) (4) *DP release testing*	(b) (4)		Waiver	OII/OBI (b) (4) NAI
(b) (4) *DP labeling*	(b) (4)		Waiver	OII/OHADI (b) (4) VAI

Acronym key: CBER – Center for Biologics Evaluation and Research; DMPQ – Division of Manufacturing and Product Quality; DP – drug product; DS – drug substance; NAI – No Action Indicated; OBI – Office of

CBER/DMPQ led a PLI of Ultragenyx Pharmaceutical Inc. in Bedford, MA from April 6 – 14, 2026. A Form FDA 483 list of observations was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER/DMPQ led a PLI of Ultragenyx Pharmaceutical Inc. in Woburn, MA from April 15 – 17, 2026. A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

OII/OBI conducted a surveillance inspection of (b) (4) from (b) (4). A Form FDA 483 list of observations was not issued, and the inspection was classified as NAI.

OII/OHADI conducted a surveillance inspection of (b) (4) from (b) (4). A Form FDA 483 list of observations was issued, and the inspection was classified VAI.

e. Container/Closure System

The drug product is filled into (b) (4) (8 mL) Type (b) (4) clear borosilicate glass vials (b) (4); part of the (b) (4) The vials are closed with 20 mm chlorobutyl rubber stoppers (b) (4) and sealed with 20 mm aluminum crimp seals equipped with a plastic flip-off cap (b) (4) performed the container closure integrity testing, employing (b) (4) method; all acceptance criteria were met.

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of GENGLYCOS will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

In vivo pharmacology studies conducted in 2-week-old glucose-6-phosphatase, catalytic subunit 1 (G6PC) (b) (4) demonstrated that IV administration of DTX401 at dose levels of 5.0×10^{11} or 1.0×10^{13} gc/kg led to dose-dependent increases in hepatic G6Pase activity and fasting glucose levels. At the higher dose level of 1.0×10^{13} gc/kg, DTX401 also improved non-fasting blood glucose, cholesterol, and triglyceride levels, and normalized fasting glucose and the hepatomegaly and nephromegaly characteristic of (b) (4) mice to levels seen in wildtype (WT) mice. The minimally effective dose identified in these studies is equivalent to 9.0×10^{11} gc/kg of DTX401. These data provide confirmatory mechanistic evidence in support of the effectiveness of DTX401.

Three separate 92-day, single-dose toxicology studies were conducted in healthy adult and juvenile mice. In adult mice, the no observed adverse effect level (NOAEL) for IV administration of DTX401 was 1.0×10^{13} gc/kg, based on findings of single-cell hepatic necrosis and Kupffer cell hypertrophy/hyperplasia at higher dose levels. In juvenile mice administered IV DTX401 on postnatal days (PNDs) 2, 14, or 28, the NOAEL was 7.0×10^{13} gc/kg. Decreasing levels of vector DNA were observed over time in the livers of mice administered DTX401 at PND 28 or younger. One 6-month, single-dose toxicology study was conducted in healthy juvenile non-human primates (NHPs) and identified a NOAEL equivalent to 1.3×10^{14} gc/kg of DTX401.

Following IV administration in mice, DTX401 biodistribution (BD) was highest in the liver and vector DNA was detected in all evaluated tissues, including the ovaries and testes, where both DTX401 DNA and RNA were detected. Intravenous administration of DTX401 at 7×10^{13} gc/kg to male or female mice prior to mating had no impact on clinical outcomes in offspring and did not result in detection of DTX401 DNA in offspring livers. Similarly, IV administration of DTX401 at 7×10^{13} gc/kg to pregnant dams at presumed gestational day (GD) 6 resulted in DTX401 DNA detection in placenta but not offspring livers, and there was no impact on embryofetal development on GD 18.

5. Clinical Pharmacology

GENGLYCOS is an adeno-associated virus serotype 8 (AAV8) based gene therapy designed to deliver a copy of the glucose-6-phosphatase (*G6PC*) gene with native human *G6PC* promoter and enhancer elements to hepatocytes, resulting in the production of normally functioning G6Pase. The clinical pharmacology evaluation of GENGLYCOS includes pharmacokinetics (biodistribution and vector shedding), pharmacodynamics (reduction in daily cornstarch intake), and immunogenicity assessment (Studies 401GSDIA01 and DTX401-CL301). After administration of GENGLYCOS, peak levels of vector genome DNA occurred at the first post-dose assessment on Day 2 in blood and between Day 3 and Day 13 in stool, saliva, and urine. Vector genome DNA was cleared from blood within approximately 24 weeks, saliva within 7 weeks and from urine and stool within 13 weeks post-infusion. Pharmacodynamic assessment includes reduction in daily cornstarch intake, which serves as a surrogate endpoint reasonably likely to predict clinical benefit. GENGLYCOS treatment resulted in statistically significant reduction in cornstarch intake compared to Placebo at Week 48 post-dosing. Refer to Section 6 for detailed review. Both humoral and cellular immune responses against GENGLYCOS were evaluated. There was no apparent impact of anti-AAV8 antibodies on efficacy or safety. The clinical significance of anti-G6Pase antibodies and G6Pase ELISpot is not clear. The Applicant's proposed dosing regimen, a single dose of GENGLYCOS at 1.0×10^{13} genome copies/kg body weight administered via intravenous (IV) infusion, is acceptable. The clinical pharmacology results support accelerated approval for GENGLYCOS 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).

6. Clinical & Statistical Evaluation

a. Clinical Studies (Efficacy)

The primary evidence of effectiveness is based on data from the Phase 3 Study DTX401-CL301. Data from phase 1/2 Study 401GSDIA01, a single-arm, open-label, 52-week, exploratory study in 12 adults with GSDIa, was considered in the safety assessment only. In Study 401GSDIA01, 9 of the 12 patients received GENGLYCOS at a dose of 6.0×10^{12} GC/kg which was determined by FDA to be analytically equivalent to the proposed commercial dose (and the dose used in the phase 3 study) of 1.0×10^{13} GC/kg based on a bridging study performed after a change in the vector genome titer assay.

Study DTX401-CL301 was a global, multicenter, randomized, double-blind, placebo-controlled study. Patients were randomized 1:1 to either a single IV infusion of GENGLYCOS (1.0×10^{13} GC/kg, capped at 90 kg) or matching placebo. The study consisted of an initial screening 16-week period of nutritional optimization (cornstarch dosing and dietary intake were modified to establish glycemic and metabolic control prior to dosing). The primary efficacy analysis was conducted at Week 48. After that, GENGLYCOS patients switched to placebo and 19 eligible placebo patients (of the original 25 patients) received GENGLYCOS for another 48 weeks (up to week 96) while maintaining blind. Starting 2 weeks after dosing, patients received either oral corticosteroids (prednisone or equivalent) at 60 mg/day (or 1.0 mg/kg/day for patients <60 kg) or matching placebo for 4 weeks. The dose was tapered over another 4 weeks and stopped.

The primary efficacy population included 46 patients with GSDIa (based on deficient G6Pase activity on liver biopsy or *G6PC* molecular genetic testing) and a mean age of 20.5 years (range 8–37 years). Patients with pre-existing anti-AAV8 capsid antibodies were excluded. The population included: 58.% male, 89.1% White, 13.0% Hispanic/Latino 4.3% Asian.

Study DTX401-CL301 met its pre-specified criteria for statistical significance on the primary and key secondary endpoints related to changes from baseline to week 48 in measures of CS intake: total daily intake and number of daily doses respectively). A numerically higher rate of hypoglycemia was observed in the GENGLYCOS group compared to the placebo group as measured by the percentage of glucose values in the hypoglycemic range (< 70 mg/dL), a secondary endpoint. The efficacy results are summarized in Table 4.

Table 4: Primary and Secondary Efficacy Results: Study DTX401-CL301

Efficacy Endpoint* (Week 48)	**GENGLYCOS (N = 21)**	**Placebo (N = 25)**	**Difference (95% CI)**
Daily Cornstarch Intake			
Baseline; Mean (SD) **(g)**	293.9 (83.2)	271.7 (109.0)	
Percent Change from Baseline, LS Mean (SE)	-41.1% (3.9%)	-10.2% (3.6%)	-30.9% (-40.8%, -20.9%)
Number of Daily Cornstarch Doses			
Baseline; Mean (SD)	5.8 (1.4)	5.1 (1.4)	
Change from Baseline, LS Mean (SE)	-1.2 (0.2)	-0.2 (0.2)	-1.0. (-1.4, -0.5)
Percentage of Glucose Values in the Hypoglycemic Range (< 70 mg/dL)			
Baseline; Mean (SD)	2.5% (2.5%)	1.9% (2.2%)	
Change from Baseline, LS Mean (SE)	3.1% (0.8%)	0.1% (0.8%)	3.1% (0.9%, 5.2%)

CI=Confidence Interval; LS=Least Square; SD=Standard Deviation; SE=Standard Error.
*The LS mean, SE, and 95% CI were estimated using a mixed model for repeated measures (MMRM).

In 15 of the 21 patients treated with GENGLYCOS with available data at Week 96, the observed mean (SD) percent change from baseline (pre-dosing) at Week 96 in daily cornstarch intake was -60.8% (19.7%) and the observed mean (SD) change from baseline (pre-dosing) at Week 96 in the number of daily cornstarch doses was -2.0 (1.3). In 19 of the 21 patients treated with GENGLYCOS with available data at Week 96, the observed mean (SD) change from baseline (pre-dosing) at Week 96 in percentage of glucose values in the hypoglycemic range (glucose <70 mg/dL) was 5.2% (6.3%).

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were conducted at one foreign and two domestic clinical investigators who participated in the conduct of study protocol DTX401-CL301. The inspections did not reveal substantive issues that impact the data submitted in this Biologics License Application (BLA).

c. Pediatrics

GENGLYCOS has orphan drug designation and, thus, is exempt from Pediatric Research Equity Act (PREA) requirements. The Phase 3 study, which serves as the primary basis of the evaluation of efficacy, included 20 pediatric patients with GSDIa aged 8-17 years (44% of the total efficacy population of N=46).

d. Other Special Populations

The efficacy of GENGLYCOS has not been studied in other special populations.

7. Safety Evaluation and Pharmacovigilance

The overall safety database in the BLA includes 58 patients with GSDIa. Of those, 55 patients (35 adults, 20 pediatric patients aged 8-17 years) were exposed to the proposed commercial dose of GENGLYCOS across two clinical studies: 46 patients in the Phase 3 study (Study DTX401-CL301; follow-up for 96 weeks) and 9 patients in the Phase 1/2 study (Study 401GSDIA01, a single-arm, open-label study of GENGLYCOS in 12 adults with GSDIa). Three additional adults were exposed to a lower dose of the product in Study 401GSDIA01 without significant differences in the safety assessment. FDA considers the safety database adequate to characterize the safety and inform the benefit-risk assessment of GENGLYCOS considering the rarity of GSDIa, and the known expected risks associated with the product's mechanism as an AAV-based gene therapy.

In Phase 3 Study DTX401-CL301, treatment-emergent adverse events (TEAEs) were reported in all 21 GENGLYCOS -treated patients (100%) compared to 22 of 25 placebo patients (88.0%) during the PEAP. There were no deaths. SAEs were more frequent in the GENGLYCOS group (8/21 patients, 38%; 10 SAEs) compared to placebo (3/25 patients, 12%; 4 SAEs). Seven serious adverse reactions (SARs) were observed during the PEAP period (48 weeks) including anaphylaxis (2 patients), adrenal insufficiency (2 patients), elevated lactate/lactic acidosis (2 patients), and hypoglycemia (1 patient). The most frequently observed TEAEs in Study DTX401-CL301 are presented in Table 5.

Table 4.Treatment-Emergent Adverse Events: Study DTX401-CL301 (N=46)

	GENGLYCOS (N=21) **Events n | Subjects N (%)**	**Placebo (N=25)** **Events n | Subjects N (%)**
ALT/AST Enzyme elevated[1]	29 | 15 (71)	6 | 3 (12)
Nausea	12 | 8 (38)	10 | 4 (16)
Headache	11 | 5 (24)	9 | 3 (12)
Hypertriglyceridemia[2]	10 | 6 (29)	2 | 2 (8)
Adrenal Insufficiency [3]	7 | 5 (24)	0 | 0
Constipation	5 | 4 (19)	0 | 0
Hyperglycemia[4]	5 | 3 (14)	0 | 0
Acne / Dermatitis Acneiform	4 | 4 (19)	0 | 0
Cushingoid Features	3 | 3 (14)	0 | 0
Anaphylaxis[5]	2 | 2 (10)	0 | 0

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.
[1]All events were mild to moderate (< 5.0× ULN), except one severe (Grade 3) asymptomatic event (peak ALT: 253 U/L). ALT/AST elevations peaked between 4 and 12 weeks post-GENGLYCOS administration and resolved within 15 weeks

[2] All events were mild to moderate (less than 2.5× ULN), 2 events were serious
[3] Two events were serious
[4] All events were mild to moderate
[5] Both events were serious

The safety profile was characterized by three primary safety signals occurring in GENGLYCOS-treated patients:

- Anaphylaxis/Infusion-Related Reactions: Two GENGLYCOS-treated patients experienced an anaphylactic reaction (10%) which occurred within 1 to 6 minutes of infusion initiation. Both required immediate discontinuation of the infusion and resolved with clinical management.
- Hepatic Toxicity: Transaminase occurred in 15 of 21 GENGLYCOS-treated patients (71%) compared to 3 of 25 placebo patients (12%). Events were predominantly Grade 1–2, asymptomatic, and managed with corticosteroids, peaking at 4–12 weeks post-administration. No patients met Hy's Law criteria for drug-induced liver injury (DILI).
- HPA Axis Suppression/Adrenal Insufficiency: Adrenal insufficiency occurred in 5 GENGLYCOS-treated patients (24%) and no placebo patients. These included 2 SAEs requiring acute medical intervention and hospitalization, one of which requiring ICU management.

Additionally, metabolic worsening was observed at higher rates in the GENGLYCOS group compared to placebo, including hypertriglyceridemia (28.6% vs. 8.0%), hyperglycemia (14.3% vs. 0%), and Cushingoid features (14.3% vs. 0%), reflecting the combined effects of GENGLYCOS treatment, concomitant corticosteroid use, and the underlying metabolic burden of GSD1a.

The safety findings from Phase 1/2 Study 401GSDIA01 are consistent with the safety profile characterized in the Phase 3 study, with no new safety signals identified.

Pharmacovigilance

The Applicant's pharmacovigilance plan (PVP) includes infusion-related reactions and hepatic reactions as important identified risks. Insertional mutagenesis and malignancy, thrombotic microangiopathy (TMA), dorsal root ganglion (DRG) and peripheral nerve effects, and the clinical consequences of hypertriglyceridemia are listed as important potential risks. Adrenal insufficiency is listed as an important potential risk associated with corticosteroid use. Areas of missing information include long-term safety and safety in pregnant or lactating women.

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80. In addition, the sponsor agreed to enhanced pharmacovigilance for malignancy for the first three years post-approval, including 1) submission of expedited (15-day) reports to FAERS for events of malignancy, regardless of seriousness or labeled status, 2) inclusion of aggregate assessments of reports of malignancy in periodic safety reports.

The Applicant will also conduct a prospective observational study to assess and characterize the long-term safety and pregnancy outcomes in patients treated with pariglasgene brecaparvovec-opnr. The study will assess the incidence of serious

adverse events, including the risk of adrenal insufficiency and malignancy as a post-marketing commitment (see section 11c, PMC #2).

The available safety data do not substantiate a need for a safety-related postmarketing requirement (PMR) or Risk Evaluation and Mitigation Strategy (REMS).

The Applicant's proposed PVP is adequate.

8. Labeling

The proposed proprietary name, GENGLYCOS, was received by the Advertising and Promotional Labeling Branch (APLB) on August 8, 2025 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 23, 2026. Proposed name suffixes were submitted on August 8, 2025 and the proposed suffix *-opnr* was found acceptable on July 23, 2026.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, package and container labels, and found them acceptable from a promotional and comprehension perspective.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. FDA and the Applicant reached agreement on the United States Prescribing Information (USPI), with revisions incorporated.

9. Advisory Committee Meeting

The submitted evidence did not raise unresolved scientific or regulatory questions that would benefit from an advisory committee discussion. Therefore, this BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee.

10. Other Relevant Regulatory Issues

GENGLYCOS has previously received Orphan Drug, Rare Pediatric Disease, Fast Track, and Regenerative Medicine Advanced Therapy designations. The BLA received priority review designation. The Applicant requested a rare pediatric disease priority review voucher (RPD PRV) under Section 529 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) which was granted upon approval.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness and sufficient evidence of safety to support accelerated approval of GENGLYCOS 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).

b. Benefit/Risk Assessment

The submitted data provides substantial evidence of effectiveness for GENGLYCOS based on a treatment effect on a surrogate endpoint, percent reduction in total daily cornstarch intake, which is reasonably likely to predict clinical benefit, including sustained reductions in total daily cornstarch doses and improvements in fasting tolerance as assessed by time to hypoglycemia (TTH) during the controlled fasting challenge (CFC).

At Week 48, GENGLYCOS demonstrated a statistically significant 31% LS mean reduction in total daily cornstarch intake versus placebo (−41.1% vs. −10.2%; $p < 0.0001$). Secondary endpoints were directionally consistent, including a reduction of approximately one cornstarch dose per day, a numerical improvement in fasting tolerance (between-group difference: 0.6 hours), and relative preservation of time in euglycemic range (−1.0%) compared to a meaningful decline in the placebo group (−6.7%). However, GENGLYCOS-treated patients have numerically higher rates of hypoglycemia (blood glucose 70-54 mg/dL), a slight increase in time in hypoglycemic range (glucose <70 mg/dL and <54 mg/dL), suggesting that restored G6Pase activity did not fully compensate for the reduction in cornstarch intake. Patient-reported outcomes reflected limited self-perceived improvement, and metabolic parameters, particularly triglycerides, trended toward worsening rather than the expected improvement associated with reduced cornstarch intake.

The observed risks include infusion-related reactions, hepatic toxicity, and HPA axis suppression/adrenal insufficiency. Metabolic worsening was also observed at higher rates in the GENGLYCOS group. The observed risks were mostly mild-moderate. The serious adverse events were manageable and resolved.

Overall, GSDIa represents a serious, progressive genetic condition with significant unmet medical need and no currently approved disease-modifying therapy. The demonstrated reduction in cornstarch intake, directionally consistent secondary findings, and disease-modifying mechanism of action collectively support a favorable benefit-risk assessment. The observed risks were mostly mild to moderate in severity. Serious adverse events were manageable and resolved. These risks are outweighed by the clinical benefits. The benefit-risk assessment is favorable and supports accelerated approval of GENGLYCOS, with ongoing verification of clinical benefit and long-term safety to be assessed through required and committed postmarketing studies.

c. Recommendation for Postmarketing Activities

Accelerated approval regulations require that the Applicant conduct adequate and well-controlled trial(s) to verify and describe the clinical benefit of GENGLYCOS. The Applicant agreed to the following PMR:

1. Conduct an adequate and well-controlled clinical study to verify and describe the clinical benefit of pariglasgene brecaparvovec-opnr in adult and pediatric patients

with glycogen storage disease type Ia (GSD Ia). The study will evaluate the efficacy of pariglasgene brecaparvovec-opnr compared to standard-of-care (SoC) management on measures of nutritional management (cornstarch intake, doses), and glycemic and metabolic control in treated patients compared to an appropriate randomized, concurrent control group of patients treated with standard-of-care management. The population should be appropriately enriched for patients who require at least 4 doses of cornstarch per day to maintain glycemic/metabolic control. The study will test the superiority of pariglasgene brecaparvovec-opnr over SoC on the co-primary endpoints: absolute change from baseline in the number of daily cornstarch (CS) doses and time to hypoglycemia (TTH) (blood glucose 70 to 54 mg/dL) during a controlled fasting challenge (CFC). Secondary efficacy endpoints (tested for superiority) should include (at minimum): absolute change from baseline in plasma triglycerides, uric acid, and lactate; change from baseline in growth parameters (weight, height/length); absolute change from baseline in number of nighttime CS doses; change from baseline in clinician-reported assessments of health and daily function (e.g., disease-specific outcome assessments, Clinician Global Impression of Severity (CGI-S), others).

Final Protocol Submission Date: December 31, 2026
Study Completion Date: August 31, 2031
Final Study Report Submission Date: December 31, 2031

The Applicant agreed to the following clinical PMCs subject to reporting requirements under section 506B:

2. Conduct 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 pre-specified 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).

   Final Protocol Submission Date: December 31, 2026
   Study Completion: November 30, 2038

   Final Study Report Submission Date: August 31, 2039

3. Conduct adequate analytical and clinical validation studies to support revisions to the labeling of pariglasgene brecaparvovec-opnr to specify the use of an FDA-authorized in vitro companion diagnostic device to accurately and reliably identify patients who do not have pre-existing anti-AAV8 antibodies and for whom pariglasgene brecaparvovec-opnr is indicated.

   Study Completion Date: February 28, 2027
   Final Study Report: May 31, 2027

   The final study report should be accompanied by a revised labeling supplement incorporating the authorized companion diagnostic device information.

The Applicant agreed to the following CMC PMC not subject to reporting requirements under section 506B:

4. Ultragenyx commits to reassessing the acceptance criteria for release testing of pariglasgene brecaparvovec-opnr drug substance for (b) (4) measured by (b) (4), and drug product for in vitro potency measured by (b) (4) and, if applicable, revising the acceptance criteria and justifications. A final acceptance criteria reassessment report will be submitted as a "Postmarketing Study Commitment – Re-assessment of Lot Release Acceptance Criteria Final Study Report" after CBER lot release of (b) (4) drug product batches for US commercial distribution.
   Final study report submission: June 30, 2029

12. References

Expedited Programs for Serious Conditions | Drugs and Biologics | FDA

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