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Applicant	Ultragenyx Pharmaceutical Inc.
Established Name	pariglasgene breca parvovec-opnr
(Proposed) Trade Name	GENGLYCOS
Pharmacologic Class	Adeno-associated virus (AAV) vector-based gene therapy
Dosage Form(s) and Route(s) of Administration	A suspension for intravenous infusion
Dosing Regimen	One-time treatment
Indication(s) and Intended Population(s)	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) Note: This indication is approved under accelerated approval based on reduction in daily cornstarch intake. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

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GLOSSARY

Abbreviation or Term	Definition
AAV8	Adeno-associated virus serotype 8
AE	Adverse event
AESI	Adverse event of special interest
CFC	Controlled fasting challenge
CGM	Continuous glucose monitoring
CI	Confidence interval
CRO	Contract research organization
CSR	Clinical study report
(b) (4)	
DMC	Data monitoring committee
DRG	Dorsal root ganglion
eCRF	Electronic case report form
eDiary	Electronic diary
FAS	Full Analysis Set
FDA	Food and Drug Administration
G6Pase	Glucose-6-phosphatase
G6PC	Glucose-6-phosphatase gene
GC	Genome copies
GCP	Good Clinical Practice
GSDIa	Glycogen storage disease type Ia
ICE	Intercurrent event
ICF	Informed consent form
IP	Investigational product
IRR	Infusion-related reaction
IRT	Interactive response technology
ITT	Intention-to-treat
IV	Intravenous
KOL	Key Opinion Leader
LS	Least squares
MAR	Missing at random
MI	Multiple imputation
mITT	Modified Intention-to-Treat Analysis Set
MMRM	Mixed model for repeated measures

Abbreviation or Term	Definition
NI	Non-inferiority
PEAP	Primary Efficacy Analysis Period
PGIC	Patient Global Impression of Change
PI	Principal investigator
PP	Per Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SMBG	Self-monitoring of blood glucose
TEAE	Treatment-emergent adverse event
TTH	Time to hypoglycemia

1. Executive Summary

This is an original Biologics License Application (BLA) for an adeno-associated virus serotype 8 (AAV8) based gene therapy GENGLYCOS (also referred to as DTX401, pariglasgene breccaparvovec-opnr), which is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years and older with glycogen storage disease type Ia (GSDIa).

The clinical studies in this submission consist of three studies: the pivotal study DTX401-CL301, the Phase 1/2 study 401GSDIA01, and the long-term follow-up study 401GSDIA02. The primary efficacy and safety evaluations were based on pivotal study DTX401-CL301.

Study Design of DTX401-CL301:

DTX401-CL301 is an ongoing Phase 3 multicenter, randomized, double-blind, placebo-controlled study where a total of 49 patients were randomized in a 1:1 ratio to receive a single intravenous infusion of either GENGLYCOS at a dose of 1.0×10^{13} genome copies per kilogram (gc/kg) body weight or placebo. Three patients discontinued prior to receiving any treatment and 46 patients received the assigned treatment. Study DTX401-CL301 comprised a 48-week, double-blind, placebo-controlled primary efficacy analysis period (PEAP; Day 1-Week 48), a 48-week, double-blind crossover period (Week 48-Week 96), and a 48-week follow-up period (Week 96-Week 144), for a total duration of 144 weeks. Data cutoff date was March 3, 2025.

Demographics:

Among 46 patients treated, the mean age was 20.5 years (range 8 to 37 years), 27 (58.7%) patients were male, 41 (89.1%) patients were White, 2 (4.3%) patients were Asian, 3 (6.5%) patients were of unknown race or did not report race, and 6 (13.0%) patients were Hispanic or Latino.

Efficacy Results:

All 46 treated patients were included for efficacy evaluation. The primary efficacy endpoint was the percent change from baseline to Week 48 in daily cornstarch (CS) intake. The least square (LS) means (standard error, SE) of percent change from baseline to Week 48 were -10.2% (3.6%) in the placebo group and -41.1% (3.9%) in the DTX401 group, resulting in a statistically significant LS mean difference (95% CI) of -30.9% (-40.8%, -20.9%) [$p < 0.0001$]. This result met the prespecified superiority criterion for the primary endpoint.

There were three secondary endpoints subject to multiplicity control. For the secondary endpoint of the number of daily CS doses, the LS mean changes from baseline to Week 48 were -1.2 in the DTX401 group and -0.2 in the placebo group (LS mean difference [95% CI]: -1.0 [-1.4, -0.5] doses; $p < 0.0001$), reaching statistical significance. However, for the secondary endpoint of percent of glucose values in the hypoglycemic range (<70 mg/dL), a greater increase in the LS mean changes from baseline to Week 48 was observed in the DTX401 group (3.1%) compared to the placebo group (0.1%), resulting an LS mean difference (95% CI) of 3.1% (0.9%, 5.2%), indicating a worse treatment

response for DTX401 relative to placebo. Although this finding fell within the pre-specified non-inferiority margin of 10%, the FDA clinical review team determined during the review that this margin was not clinically justifiable, and an appropriate margin for this endpoint could not be established at the time of pre-specification.

There was no statistically significant difference between the two treatment groups in the third secondary endpoint, Patient Global Impression of Change (PGIC).

Finally, the findings were inconclusive for time to hypoglycemia (TTH) during the controlled fasting challenge (CFC), a protocol-defined exploratory secondary endpoint of particular clinical interest.

Safety Results:

During PEAP, 4 serious treatment-emergent adverse events (TEAEs) were reported in 3 (3/25; 12.0%) patients in the placebo group and 10 serious TEAEs were reported in 8 (8/21; 38.1%) patients in the DTX401 group. Twelve serious TEAEs were reported in 9 patients (9/19; 47.4%) in the Crossover Placebo→DTX401 group after DTX401 treatment, and a total of 25 serious TEAEs in 12 (12/21; 57.1%) patients were reported in the DTX401 group during crossover period and follow-up period. No deaths occurred during the study.

Conclusion:

Collectively, while DTX401 demonstrates a reduction in cornstarch intake, it is also associated with a slight increase in the risk of hypoglycemia. The clinical effectiveness remains highly uncertain and, given the totality of evidence, the benefit-risk profile is difficult to characterize. Nevertheless, in the context of a rare disease with limited therapeutic options and a significant unmet medical need, accelerated approval may be appropriate, with a post-marketing requirement to verify clinical benefit through a confirmatory trial.

2. Clinical and Regulatory Background

This original Biologics License Application (BLA) is a marketing application for GENGLYCOS (also referred to as DTX401), an AAV8-based gene therapy, for the indication to reduce daily cornstarch intake as an adjunct to nutritional management in patients 8 years and older with glycogen storage disease type Ia (GSDIa).

2.1 Disease or Health-Related Condition(s) Studied

GSDIa is a rare, serious, and potentially life-threatening disease due to an inborn error of carbohydrate metabolism caused by pathogenic biallelic variants of the glucose-6-phosphatase (*G6PC*) gene.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

GSDIa disease management is currently centered around avoidance of hypoglycemia and metabolic derangement and minimizing acute and long-term complications. Standard of care for GSDIa patients comprises exogenous glucose replacement therapy, most commonly in the form of uncooked cornstarch, administered as prescribed scheduled doses as frequently as every 3 to 4 hours. Patients need to follow a highly regimented, medically prescribed diet, avoid fasting and frequently monitor blood glucose levels.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

DTX401 is currently not authorized for marketing in any country.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 Regulatory Activity

Date	Regulatory Activity
January 31, 2023	Type B Meeting (CRMTS #14509): FDA conveyed that a primary endpoint of percent change in daily cornstarch intake is not adequate as a standalone primary endpoint and recommended co-primary endpoints of cornstarch intake and time to hypoglycemia measured by the controlled fasting challenge (CFC). FDA also suggested Ultragenyx to support the definitions of clinically meaningful change in both coprimary endpoints with data-driven arguments. The applicant disagreed with the FDA's stance regarding the clinical meaningfulness of CFC as a co-primary endpoint. Consequently, FDA's suggestions were not incorporated in the protocol.
December 05, 2024	Pre-BLA Meeting (Meeting #20727): FDA agreed cornstarch reduction may be clinically meaningful; FDA provided guidance on presentation of clinical, nonclinical, and CMC content to support the BLA submission and assessment of benefit-risk for DTX401 during the BLA review.

Source: Adapted BLA 125858/0, Module 1.6.3, Summary of FDA Milestones and Interactions.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized to conduct a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

To support the application, the applicant submitted clinical results from three studies: the Phase 1/2 study 401GSDIA01, the long-term follow-up study 401GSDIA02, and Phase 3 Study DTX401-CL301. My review will focus on Study DTX401-CL301, the primary source of evidence for the efficacy and safety of DTX40 submitted in support of this application.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical review includes documents in the original BLA 125858/0 and information request (IR) responses from the Applicant submitted as BLA amendments. Documents reviewed are listed below:

- STN 125858/0.0 Module 1
- STN 125858/0 Module 2.5 Clinical Overview
- STN 125858/0 Module 2.7.3 Summary of Clinical Efficacy
- STN 125858/0 Module 2.7.6 Synopses of Individual Studies
- STN 125858/0 Module 5.2 Tabular Listing of all Clinical Studies
- STN 125858/0 Module 5.3.5 Reports of Efficacy and Safety Studies
- STN 125858/0.13 Module 1.11.3 Clinical Information Amendment - Response to FDA Clinical Information Request
- STN 125858/0.19 Module 1.11.3 Clinical Information Amendment - Response to FDA Clinical Information Request
- STN 125858/0.42 Module 1.11.3 Clinical Information Amendment - Response to FDA Clinical Information Request

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the three studies submitted to the BLA: the Phase 3 study DTX401-CL301, Phase 1/2 study 401GSDIA01, and long-term follow-up study 401GSDIA02.

Table 2 Overview of Clinical Studies

Study Identifier	Study Design and Objective of the Study	Planned Dosage Regimen; Route of Administration	Study Population; Number of Patients; Study Duration	Study Status;
DTX401-CL301	Study Design: Phase 3, randomized, double-blind, placebo-controlled efficacy and safety study. Objective: To evaluate the efficacy of DTX401 to	Dose Regimen: Single dose of DTX401 (1.0×10^{13} genome copies per kilogram [gc/kg]) Route of Administration: IV infusion	Study Population: Patients ≥ 8 years of age with confirmed diagnosis of GSDIa, with optimized and stable nutrition, glycemic, and clinical status. Number of Patients: - 49 patients enrolled and randomized; - 46 patients dosed with blinded IP on Day 1;	Ongoing; Week 96 analysis complete.

Study Identifier	Study Design and Objective of the Study	Planned Dosage Regimen; Route of Administration	Study Population; Number of Patients; Study Duration	Study Status;
	reduce or eliminate dependence on exogenous glucose replacement therapy needed to maintain glucose control.		- 36 patients dosed with blinded IP at Week 48. Study Duration: - Screening period: up to 16 weeks - Randomization period: 10 days - Primary Efficacy Analysis Period (PEAP): 48 weeks - Crossover Period: 48 weeks - Follow-up Period: 48 weeks	
401GSDIA01	Study Design: Phase 1/2 Open-label, single-arm, multicenter, safety, and dose-finding study; Objective: To determine the safety of single IV doses of DTX401 in adults with GSDIa, including the incidence of DLTs	Dose Regimen: Cohort 1: 2.0×10^{12} GC/kg (reactive steroid regimen) Cohort 2: 6.0×10^{12} GC/kg (reactive steroid regimen) Cohort 3: 6.0×10^{12} GC/kg (optimized reactive steroid regimen) Cohort 4: 6.0×10^{12} GC/kg (prophylactic steroid regimen) Route of Administration: Single dose, IV infusion	Study Population: Adult patients ≥ 18 years of age with GSDIa. Number of Patients: 12 total patients; 3 patients in each cohort. Study Duration: Screening period: up to 8 weeks Follow-up period: 52 weeks following DTX401 administration	Complete
401GSDIA02	Study Design: Long-term extension of Phase 1/2 study No IP administered. Objective: To determine the long-term safety of DTX401 following a single IV dose in adults with GSDIa.	No IP infusion.	Study Population: Patients who received DTX401 in Study 401GSDIA01 Number of Patients: 12 patients. Study Duration: Up to 6 years after administration of DTX401 in Study 401GSDIA01	ongoing; last patient last visit in Feb 2025 (clinical cutoff date: 27 June 2024).

IV= Intravenous; IP=Investigational product.

Source: Adapted from BLA 125858.0, Module 5.2, Tabular Listing of All Clinical Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study DTX401-CL301

Study DTX401-CL301 is entitled “A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Adeno-associated Virus Serotype 8-mediated Gene Transfer of Glucose-6-phosphatase in Patients With Glycogen Storage Disease Type Ia.”

6.1.1 Objectives and Endpoints

Table 3 presents the primary and secondary study objectives and corresponding endpoints.

Table 3 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of DTX401 to reduce or eliminate dependence on exogenous glucose replacement therapy needed to maintain glucose control	Percent change from Baseline to Week 48 in daily cornstarch intake
Secondary (subject to multiplicity)	
To evaluate the effect of DTX401 on reducing the frequency of exogenous glucose replacement therapy	Change from Baseline to Week 48 in number of total daily doses of cornstarch
To evaluate the effect of DTX401 on glucose control	Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (<70 mg/dL [3.9 mmol/L]), assessed for non-inferiority with a non-inferiority margin of 10%; if non-inferiority is established, the endpoint will be tested for superiority
To evaluate the effect of DTX401 on patient experience of disease	PGIC assessment score at Week 48
Secondary (not subject to multiplicity)	
To evaluate the effect of DTX401 on glucose control	- Change from Baseline to Week 48 in time to hypoglycemia (<54 mg/dL [3.0 mmol/L]) during the CFC - Change from Baseline to Week 48 in percentage of glucose values in the range of 70–120 mg/dL (3.9–6.7 mmol/L), assessed for non-inferiority with a non-inferiority margin of 15%; if non-inferiority is established, the endpoint will be tested for superiority
To evaluate the safety of DTX401	Incidence, severity, and relationship to investigational product of TEAEs, TEAEs of special interest, serious TEAEs, related TEAEs, discontinuations from study or investigational product due to AEs, and fatal AEs

AE=Adverse event; CFC=Controlled fasting challenge; PGIC= Patient Global Impression of Change; TEAE= Treatment-emergent adverse event.

Source: Adaptive from BLA 125858/0, DTX401-CL301 Protocol, Table 7, p55.

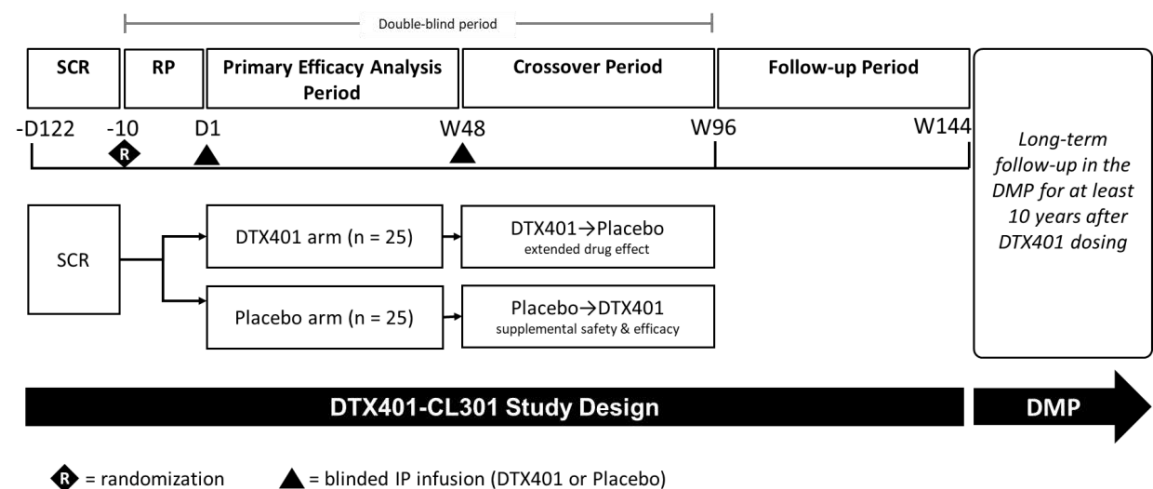
6.1.2 Design Overview

- The study planned to enroll approximately 50 patients and randomly assign them to DTX401 or placebo in a 1:1 ratio, including approximately 20 patients 8 to 17 years of age. Randomization was stratified by age (< 18 years vs ≥ 18 years) and Baseline percentage of values in the target blood glucose range (< 60%, ≥ 60% and ≤ 85%, > 85%). The study scheme is shown in

Figure 1. The sequential stages of the study included:

- **Screening (Day -122 to Day -10):** informed consent, eligibility, review of the patient's current diet, cornstarch regimen, and glycemic control
 - Nutrition Optimization Period: adjustment of the cornstarch dosing and diet to minimize the occurrence of hypoglycemia while avoiding excessive cornstarch consumption
 - Nutrition Stabilization Period: demonstration of at least 4 consecutive weeks of glycemic, diet, and cornstarch stability prior to randomization
- **Randomization Period (Day -10 to Day 0):** random assignment of patients by the interactive response technology (IRT) system. Investigators, site staff, patients and the Sponsor were blinded to IRT treatment assignment.
- **Baseline (Day 0):** admission of the patient for baseline assessments
- **Day 1 IP Administration:** administration of a single, blinded, peripheral intravenous infusion of DTX401 at 1.0×10^{13} GC/kg or placebo (saline)
- **Day 15:** administration of oral prophylactic prednisolone regimen (or matching oral placebo regimen) to minimize potential hepatic reactions (e.g., transaminase elevations)
- **Primary Efficacy Analysis Period (PEAP; Day 1 to Week 48):** the PEAP was the time from Day 1 post-dose through the completion of the Week 48 CFC. The primary endpoint and secondary efficacy endpoints would be analyzed after the last enrolled patient completes the Week 48 assessments.
- **Week 48 IP Administration:** administration of second blinded infusion of investigational product to eligible patients. Patients assigned to DTX401 at Baseline received placebo, and eligible patients assigned to placebo at Baseline received DTX401.
- **Crossover Period (double-blind; Week 48 – Week 96):** study assessments during the Crossover Period and Follow-up Period further characterized the efficacy and safety of DTX401 administration to inform the overall risk-benefit profile. The patients, investigators, site study teams and a dedicated site-facing sponsor study team remained blinded until the last patients completed their Week 96 visit or early withdrawal visit.
- **Follow-up Period (Week 96 through Week 144)**

Figure 1 Study Scheme



D=Day; DMP=Disease monitoring program; RP=Randomization period; SCR=Screening; W=Week
Source: BLA 125858/0, Clinical Study Report, Figure 1, p35.

6.1.3 Population

Patients who were ≥ 8 years of age and were confirmed diagnosis of GSDIa by deficient enzymatic activity (on liver biopsy), or by molecular testing of *G6PC* gene revealing 2 pathogenic mutations (or 1 pathogenic mutation in the absence of characteristic features of GSDIb).

6.1.4 Study Treatments or Agents Mandated by the Protocol

An overview of all interventions is provided in Table 4. The study treatments in this study include the investigational products (DTX401 and placebo), the oral prophylactic prednisolone regimen (or matching oral placebo regimen) initiated on Day 15, and premedications administrated before IP infusion.

Table 4 Study Interventions

Intervention	DTX401/Placebo	Prednisolone /Placebo	Acetaminophen/ Paracetamol	2 nd generation H1 antagonist (cetirizine or equivalent)	H2 antagonist (famotidine or equivalent)
Dose formulation	(b) (4)	5 mg or 10 mg gelatin capsules / Matching placebo	Tablet	Tablet	Tablet
Unit dose strength/ dosage level	1×10^{13} GC/kg, single infusion/ NA	Weight-based dose administered over 4 weeks and tapered over 4 weeks/ NA	12.5 mg/kg, up to max dose of 1 g	10 mg for cetirizine	0.5 mg/kg, up to max dose of 40 mg for famotidine
Route of administration	IV infusion	Oral	Oral	Oral	Oral
Use	Experimental agent/ placebo comparator to DTX401	Prophylaxis: minimization and/or management of hepatic reactions ^b	Premedication prior to dosing with IP ^c	Premedication prior to dosing with IP ^c	Premedication prior to dosing with IP ^c

^a Target concentration measured using a (b) (4) method; release acceptance criteria: (b) (4)

(b) (4)

^b Described as vector-induced hepatic effects in the study protocol.

^c The study site supplied premedication that was obtained locally

(b) (4); GC=Genome copies; kg=IP=Investigational product;

IV=Intravenous; NA=Not applicable

Source: BLA 125858/0, Clinical Study Report, Table 2, p38.

6.1.6 Sites and Centers

The study was conducted at 17 centers: 9 sites in United States, 2 sites in Italy, 1 site each in Brazil, Canada, Denmark, Germany, Netherlands, and Spain.

6.1.7 Surveillance/Monitoring

Independent Data Monitoring Committee (DMC) was responsible for monitoring patients' safety throughout the course of the study. An unblinded contract research organization (CRO) medical monitoring team with oversight from a Central Independent Committee (CIC) reviewed glucose trends, cornstarch and diet and liver enzyme data to provide safety oversight to investigators on cornstarch and prednisolone management.

Please refer to the clinical review memo for more details.

6.1.8 Endpoints and Criteria for Study Success

Please refer to Table 3 for the list of efficacy endpoints.

The success criterion for the primary endpoint would be met if the treatment effect of DTX401 compared to placebo is statistically significant.

For the secondary efficacy endpoints subject to multiplicity control, superiority tests were to be performed for two of the three endpoints: the change from baseline to Week 48 in the total daily cornstarch dose and the PGIC assessment score at Week 48.

For the endpoint - the change from baseline to Week 48 in the percentage of glucose values in the hypoglycemic range (<70 mg/dL) -, non-inferiority test with a of 10% was planned.

Reviewer's comment: The applicant derived this 10% non-inferiority margin via a simulation-based method (with assumptions derived from historical data) and Key Opinion Leader (KOL) input, and they noted that the standard non-inferiority (NI) margin derivation framework could not be applied, as no placebo-controlled trials of cornstarch in GSDIa existed. During BLA review, the FDA review team determined that this NI margin was not clinically justified and did not agree with its use. Similar considerations apply to all other endpoints related to the evaluation of glucose control.

6.1.9 Statistical Considerations & Statistical Analysis Plan (SAP)

6.1.9.1 Analysis Sets:

- Screened Set: All patients who signed informed consent form (ICF)
- Full Analysis Set (FAS, all-randomized): All randomized patients
- Safety Analysis Set: All patients treated with study IP (including partial dose). Safety analyses will be performed on the Safety Analysis Set.
- Intention-to-Treat (ITT, all-treated): All randomized patients received any IP (including partial dose)
- Modified Intention-to-Treat (mITT): All randomized patients who received any IP (including partial dose) and provided at least one post-dosing assessment pertaining to primary efficacy analysis (i.e., at least one assessment of daily cornstarch intake in 1 week period prior to any of the visits at Week 24, 30, 36, 40, 42, and 48). All primary efficacy analyses will be performed on the mITT set.
- Per Protocol (PP): Excludes mITT patients with major protocol deviations that may impact primary and secondary efficacy analyses. Supplemental analyses will be performed on the PP analysis set.

Reviewer's comments:

- *The applicant used unconventional terminology for FAS and ITT; the conventional usage would be the reverse. To avoid confusion, this review uses the terms **all-randomized** and **all-treated** to refer to the applicant-defined FAS and ITT populations, respectively.*

- *The SAP pre-specified the mITT as the primary efficacy analysis population. The all-randomized population is typically preferred for primary analyses, as it most closely aligns with the intent-to-treat ITT principle; however, three untreated subjects withdrew during the study prior to dosing due to failure to meet the eligibility or baseline stability criteria. Under these circumstances, the FDA review team considers it more appropriate to base the primary analyses on the all-treated population rather than the SAP-specified mITT population. Because residual risk of bias cannot be entirely excluded, the robustness of the results will be evaluated through supplementary analyses using different definitions of analysis population.*

6.1.9.1.2 Sample Size Determination:

Regarding the primary endpoint, a planned sample size of 50 patients (25 per group) was estimated to provide approximately 91% power to detect a difference between the DTX401 and placebo. The power calculation was based on a two-sided significance level of 0.05 and assumed average reductions in cornstarch requirement of 50% in the DTX401 group and 10% in the placebo group at Week 48, with a common standard deviation of 40%, a correlation coefficient of 0.4 between assessments, and a 10% discontinuation rate at Week 48.

6.1.9.3 Multiplicity Adjustment:

A two-sided overall type I error rate of 0.05 was used for hypothesis testing of the primary and key secondary endpoints. If the primary endpoint was met, the three key secondary endpoints would be tested using the Hochberg procedure. If high negative correlations were observed in the study, Holm method would be used for multiplicity adjustment.

6.1.9.4 Primary Endpoint Analysis:

Primary Estimand:

Table 5 Primary Estimand Attributes

Attribute	Description
Population	Adults and pediatric ≥ 8 years with GSDIa
Treatment	Patients randomized to DTX401 vs Placebo
Endpoint	Percent change from Baseline to Week 48 in daily cornstarch intake
Intercurrent Events & Strategies	Intercurrent Event 1: Transient changes in dietary management or nutritional intake due to acute events, such as trauma, surgery, infection, metabolic decompensation, etc. <i>Strategy:</i> Treatment policy strategy, no adjustment will be made for the results. Intercurrent Event 2: Persistent changes in dietary management or nutritional intake due to intentional or foreseeable physiologic changes, such as seasonal changes in activity, a new weight loss regimen, exercise program, puberty, pregnancy, etc. <i>Strategy:</i> Treatment policy strategy, no adjustment will be made for the results. Intercurrent Event 3: Sub-acute changes in glucose homeostasis due to adjustments in corticosteroid dose or other medications affecting glucose homeostasis, such as insulin. <i>Strategy:</i> Treatment policy strategy, no adjustment will be made for the results. Intercurrent Event 4: Partial dosing i.e., IP infusion stopped before completion and was not resumed due to adverse event (e.g., infusion related reaction) or technical issues. <i>Strategy:</i> Treatment policy strategy, no adjustment will be made for the results.
Population-level Summary	Difference in mean percent change from Baseline between treatment groups at Week 48

IP= Investigational product.

Source: Adapted from BLA 125858/0, Statistical Analysis Plan, Table 2, p16.

Null Hypothesis:

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

Analysis Method:

For each post-baseline visit, the average of total daily cornstarch intake (including Glycosade) reported in the electronic diary (eDiary) over 1 week prior to the visit Week 24, 30, 36, and 42 was calculated, and an average over 4 weeks of data prior to Week 48 and Baseline was calculated.

A mixed model for repeated measures (MMRM) model was to be used. In this model, treatment group, average cornstarch intake at baseline, age (< 18 years vs ≥ 18 years), and baseline percentage of values in the glucose range of 60 to 120 mg/dL ($< 60\%$, $\geq 60\%$ and $\leq 85\%$, $> 85\%$), study visit, and the visit-by-treatment interaction were to be included as covariates. Compound symmetry would be used as covariance structure. Restricted maximum likelihood for the estimation. Kenward-Roger approximation would be used to adjust the degrees of freedom. Least square (LS) mean difference (DTX401 –

Placebo) at Week 48 and associated 95% confidence interval (CI) were to be estimated, with the two-sided p-value for the comparison.

Sensitivity Analyses:

Multiple sensitivity/supplementary analyses were planned to evaluate the robustness of the results to missing data, analysis methods, and handling of intercurrent events, including:

- **Analysis 1 (4/7 rule):** This analysis would include data only from those weeks where cornstarch intake was reported at least 4 out of 7 days
- **Analysis 2 (MI under MAR):** Multiple Imputation (MI) would be used to estimate the missing endpoint data at Week 24, 30, 36, 42, and 48 under assumption of missing at random (MAR). MMRM would be performed on each multiply imputed dataset, and results (p-values) will be combined using PROC MIANALYZE.
- **Analysis 3 (Tipping Point):** Tipping point would be used to impute missing endpoint data at Week 24, 30, 36, 42, and 48 under the assumption of missing not at random (MNAR). It imputed missing endpoint data (i.e., percent change from Baseline in cornstarch intake) under the MAR assumption for both groups, and imputed endpoint values for missing data in DTX401 group were further shifted (increased) by delta (i.e., reduction in efficacy of DTX401 group) until loss of significance of the treatment difference was observed (this delta was termed as a tipping point).
- **Analysis 4 (Intercurrent events handling):** Use MI to impute the results post intercurrent event (ICE).
- **Analysis 5:** Use median instead of mean cornstarch intake

6.1.9.5 Key Secondary Efficacy Endpoints Analysis (subject to multiplicity):

A similar analysis approach (MMRM model) to that used for the primary endpoint was to be applied to each of the three key secondary endpoints:

- (1) Change from baseline to Week 48 in number of total daily doses (frequency) of cornstarch
- (2) Change from baseline to Week 48 in percentage of glucose values in hypoglycemic range (< 70 mg/dL)
- (3) PGIC score at Week 48

6.1.9.6 Secondary Efficacy Endpoints Analysis (Not subject to multiplicity):

Similar MMRM model was planned for the two endpoints and the additional supplementary analyses below.

- (1) Change from Baseline to Week 48 in Time to Hypoglycemia During the CFC

Supplementary analyses:

- **Normalized time to hypoglycemia (TTH) by the amount of carbohydrates in cornstarch given prior to CFC:** the Applicant proposed that since the amount of individualized cornstarch used for the CFC would vary across patients, a supplementary analysis would be performed on normalized TTH by the amount of carbohydrates in cornstarch given prior to CFC. Specifically, the MMRM model would perform by repeated measures on the change from baseline in TTH/CS during the CFC at Weeks 36, and 48, where TTH/CS is TTH (in minutes) divided by amount of carbohydrates (in grams) in cornstarch.

Reviewer's comment: The proposed normalization of TTH by the amount of carbohydrates in the pre-CFC cornstarch dose (TTH/CS) is not a standard analytical approach. The review team finds the interpretation of this metric difficult.

- **Time between a glucose level of 70 mg/dL (3.9 mmol/L) to < 54 mg/dL (3.0 mmol/L) during the CFC from baseline:** This was based on venous blood glucose values collected in local lab data.

(2) Change from Baseline to Week 48 in Percentage of Glucose Values in the range of 70-120 mg/dL

6.1.9.7 Subgroup Analysis:

Descriptive statistics of primary and secondary endpoints would be provided for the following subgroups:

- Age (< 18 years vs $\geq$ 18 years)
- Baseline percentage of values in the glucose range of 60 to 120 mg/dL (< 60%, $\geq$ 60% and $\leq$ 85%, > 85%)
- Pubertal stage status at baseline as per the Tanner pubertal stage development scale for pediatric patients.
- Geographical region (e.g., North America, Europe, South America, Asia, etc.)
- Patients who had detectable AAV8 antibodies at baseline visit (Day 0 visit for patients treated in PEAP and Week 48 visit for patients treated in FUAP).
- Patients dosed with <4 and $\geq$ 4 average number of total daily doses of cornstarch (including Glycosade) at baseline (Primary endpoint only).
- Patients using Glycosade (Yes/No) at baseline (Primary endpoint only).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 79 patients were screened, of which 49 were enrolled and randomized into the study. Of the 49 randomized patients, 46 (93.9%) received blinded IP at the Day 1 visit. Of the 46 dosed patients, 44 patients provided at least one post-dosing assessment.

6.1.10.1.1 Demographics

Demographics and baseline disease-specific characteristics of the treated patients are presented in Table 6. Most of patients enrolled in this study were White (41/46; 89.1%).

Patients were evenly distributed between age group (pediatric patients [20/46; 43.5%] vs. adult patient) and sex (Male: 27/46; 58.7%). All demographics and baseline characteristics were comparable between the two treatment groups.

Table 6 Patient Demographics and Baseline Characteristics (All-Treated Population)

Parameter	Placebo (N = 25)	DTX401 (N = 21)	Total (N = 46)
Age at consent (years)			
Mean (SD)	20.8 (8.4)	20.2 (8.5)	20.5 (8.4)
Min, Max	8, 37	9, 32	8, 37
Age group at consent, n (%)			
8 - 17 years	10 (40.0)	10 (47.6)	20 (43.5)
≥ 18 years	15 (60.0)	11 (52.4)	26 (56.5)
Sex, n (%)			
Male	13 (52.0)	14 (66.7)	27 (58.7)
Female	12 (48.0)	7 (33.3)	19 (41.3)
Race, n (%)			
Asian	2 (8.0)	0	2 (4.3)
White	23 (92.0)	18 (85.7)	41 (89.1)
Not reported	0	2 (9.5)	2 (4.3)
Unknown	0	1 (4.8)	1 (2.2)
Ethnicity, n (%)			
Hispanic or Latino	3 (12.0)	3 (14.3)	6 (13.0)
Not Hispanic or Latino	17 (68.0)	16 (76.2)	33 (71.7)
Not Reported	5 (20.8)	2 (9.5)	7 (15.2)
Region, n (%)			
North America	17 (68.0)	13 (61.9)	30 (65.2)
Europe	6 (24.0)	6 (28.6)	12 (26.1)
South America	2 (8.0)	2 (9.5)	4 (8.7)
Baseline percentage of values in target blood glucose range (60 - 120 mg/dL), n (%)			
< 60%	5 (20.0)	5 (23.8)	10 (21.7)
≥ 60 % and ≤ 85%	15 (60.0)	13 (61.9)	28 (60.9)
> 85%	5 (20.0)	3 (14.3)	8 (17.4)

SD=Standard deviation.

Source: BLA 125858/0, Clinical Study Report-tfL, Table 14.1.2.1.1, p11.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

GSDIa diagnostic history and GSDIa disease management are presented in Table 7. All patients (46 [100%]) reported a history of taking cornstarch for the management of their GSDIa, and most patients (36 [78.3%]) reported a history of taking Glycosade to manage their GSDIa.

Table 7 GSDIa Diagnostic History and GSDIa Disease Management (All-Treated Population)

Parameter	Placebo (N=25)	DTX401 (N=21)	Total (N=46)
Age at Diagnosis of GSDIa (years)			
Mean (SD)	0.8 (1.8)	0.6 (1.3)	0.7 (1.6)
Ever Taken uncooked cornstarch for management of GSDIa - n (%)			
Yes	25 (100.0)	21 (100.0)	46 (100.0)
- Cornstarch	23 (92.0)	19 (90.5)	42 (91.3)
- Uncooked starch (excluding Glycosade)	2 (8.0)	2 (9.5)	4 (8.7)
No	0	0	0
Currently Taking Starch for Management of GSDIa - n (%)			
Yes	24 (96.0)	19 (90.5)	43 (93.5)
No	1 (4.0)	2 (9.5)	3 (6.5)
Ever Taken Glycosade for management of GSDIa - n (%)			
Yes	19 (76.0)	17 (81.0)	36 (78.3)
No	6 (24.0)	4 (19.0)	10 (21.7)
Currently taking Glycosade for management of GSDIa - n (%)			
Yes	11 (44)	8 (38.1)	19 (41.3)
No	8 (32.0)	8 (38.1)	16 (34.8)
Have ever used a feeding tube - n (%)			
Yes	18 (72.0)	15 (71.4)	33 (71.7)
No	7 (28.0)	6 (28.6)	13 (28.3)
Currently use a feeding tube - n (%)			
Yes	4 (16.0)	6 (28.6)	10 (21.7)
No	21 (84.0)	15 (71.4)	36 (78.3)

n=Number of patients; SD=Standard deviation.

Source: Adapted from BLA 125858/0.42, Tables for Response to FDA Clinical Information Request Received on 20Jul2026, Table 14.1.2.2.2.1a, Table 14.1.2.2.2.3a, pp26-27.

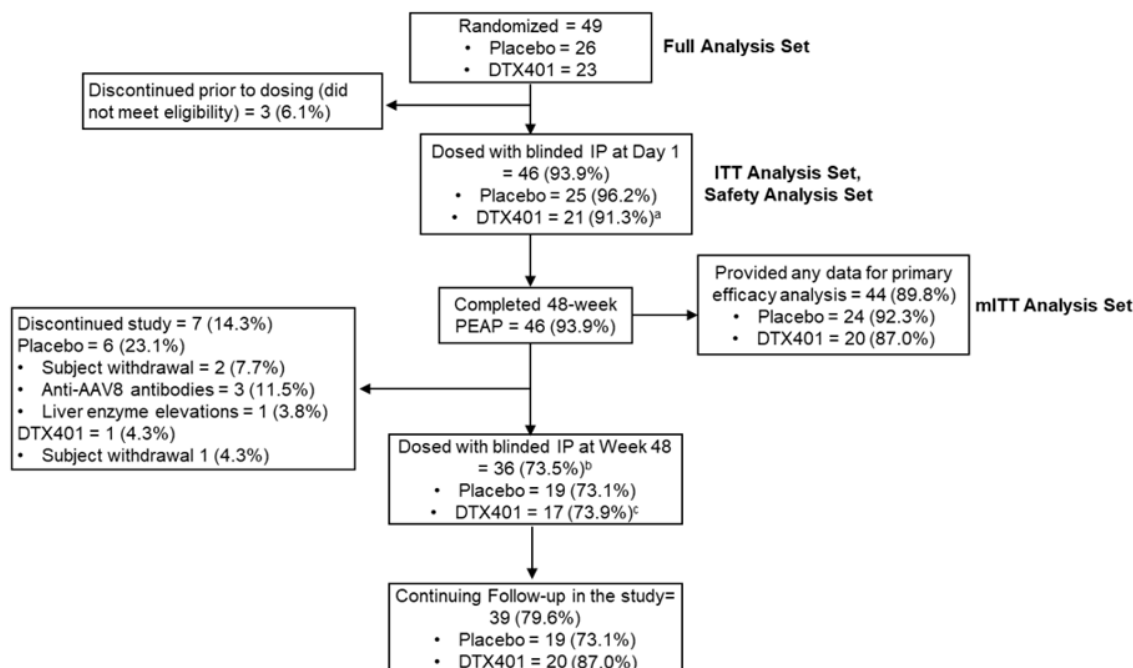
6.1.10.1.3 Patient Disposition

The patient disposition is depicted in Figure 2.

Of the 49 randomized patients, 46 received blinded IP at the Day 1 visit. Of the 3 patients who discontinued prior to receiving blinded IP, 2 did not meet eligibility criteria at baseline due to elevated non-fasting triglycerides, and 1 did not meet the stability criterion at baseline. Of the 46 dosed patients, 44 patients provided at least one post-dosing assessment for primary efficacy analysis. Two dosed patients who did not provide the post-dosing assessment included one patient from the DTX401 group who had an infusion-related reaction and continued in the study for safety follow-up only (no efficacy assessments completed) and one patient from the Placebo group who did not provide efficacy data for primary analysis due to patient preference and study burden.

All 46 patients who received blinded IP completed the 48-week PEAP. Following the PEAP, seven patients discontinued the study, and three patients in the DTX401 group did not receive blinded IP at Week 48 but are continuing in the study for follow-up. Therefore, 36 patients received blinded IP at Week 48, and a total of 39 patients were being followed up as of the data cutoff date of 03 March 2025.

Figure 2 Disposition of Patients



^a Includes 2 patients who were partially dosed.

^b At Week 48, patients in the Placebo group received DTX401 and patients in the DTX401 group received placebo.

^c Three patients from the DTX401 group did not dose with IP at Week 48, but continued follow-up in the study.

IP=Investigational product; ITT=Intent-to-treat; mITT=Modified intent-to-treat; PEAP=Primary Efficacy Analysis Period.

Source: BLA 125858/0, Clinical Study Report, Figure 2, p56.

6.1.11 Efficacy Analyses

6.1.11.1 Analysis of Primary Endpoint

The percent change from baseline in daily cornstarch intake is presented in Table 8. For the mITT population, at Week 48, the LS mean percent changes were -10.4% in the Placebo group and -40.9% in the DTX401 group. The LS mean difference [DTX401-Placebo] (95% CI) was -30.6% (-42.0%, -19.1%) ($p < 0.0001$). This result met the prespecified superiority criterion of statistical significance at a two-sided 0.05 level.

Table 8 Daily Cornstarch Intake (g) (mITT Population)

Visit	Placebo (N = 24)	DTX401 (N = 20)
Baseline		
n	24	20
Mean (SD)	268.4 (110.0)	294.1 (85.3)
Week 24		
n	24	20
Mean (SD)	242.5 (113.3)	205.2 (78.0)
%CFB, Mean (SD)	-9.73 (20.12)	-31.00 (15.24)
Week 36		
n	22	19
Mean (SD)	250.7 (112.0)	182.7 (68.3)
%CFB, Mean (SD)	-7.24 (19.89)	-36.44 (18.66)
Week 48		
n	23	19
Mean (SD)	239.1 (112.0)	171.1 (70.9)
%CFB, Mean (SD)	-10.05 (18.04)	-40.93 (18.36)
<i>MMRM Estimates</i>		
%CFB LS Mean (SE)	-10.4 (4.1)	-40.9 (4.6)
95% CI	(-18.7, -2.1)	(-50.1, -31.8)
%CFB LS Mean Difference (SE) [DTX401-Placebo]	-30.6 (5.7)	
95% CI	(-42.0, -19.1)	
p value	<0.0001	

CI=Confidence interval; LS=Least squares; mITT=Modified intent-to-treat; %CFB = Percent change from baseline; MMRM=Mixed-model for repeated measures; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report, Table 8, p69.

The analysis results based on all randomized, all-treated, and per-protocol populations showed similar findings (Table 9). For all-treated population, using the MMRM model, the LS mean (standard error; SE) percent change from baseline to Week 48 in total daily cornstarch intake was -10.2% (3.6) % in the placebo group compared with -41.1% (3.9) % in the DTX401 group (LS mean difference [95% CI]: -30.9% [-40.8%, -20.9%], $p < 0.0001$).

Table 9 Percent Change of Daily Cornstarch Intake from Baseline (CFB) for All-Randomized, All-Treated, and Per-Protocol Populations

	Placebo	DTX401	Difference [DTX401-Placebo] (95% CI; p-value)
All-Randomized	N=26	N=23	
Baseline (g), mean (SD)	269.5 (107.4)	281.8 (89.9)	
% CFB at Week 48, LS Mean (SE)	-10.3 (3.5)	-40.9 (3.8)	-31.6 (-40.2, -21.0); p<0.0001
All-Treated	N=25	N=21	
Baseline (g), mean (SD)	271.7 (109.0)	293.9 (83.2)	
% CFB at Week 48, LS Mean (SE)	-10.2 (3.6)	-41.1 (3.9)	-30.9 (-40.8, -20.9); p<0.0001
Per-Protocol Population	N=23	N=18	
Baseline (g), Mean (SD)	266.0 (111.9)	293.3 (89.8)	
%CFB at Week 48, LS Mean (SE)	-9.7 (4.2)	-41.5 (4.7)	-31.9 (-43.7, -20.1); (p<0.0001)

CI=Confidence interval; LS=Least square; SD=Standard deviation; SE=Standard error;

%CFB = Percent change from baseline.

The LS Mean, LS Mean Difference, SE, 95% CI and 2-sided p-value are from MMRM (mixed-model for repeated measures) which includes percent change from baseline in daily cornstarch intake as the dependent variable, stratification factors, visit, treatment, and visit by treatment as fixed factors and adjusted for baseline measurement.

Source: BLA 125858/0, Clinical Study Report-tfl, Tables 14.2.1.1.5.1 through 14.2.1.1.5.3, pp497-519.

Reviewer's comment:

I used the multiple imputation method and obtained similar results. Using the all-treated population, the LS means for percent change from baseline to Week 48 are -40.7% and -10.0%, with the difference (95% CI) of -30.7% (-41.9%, -19.7%).

Sensitivity Analyses

Sensitivity analyses are presented in Table 10. The results are consistent with the primary analysis.

Table 10 Sensitivity Analyses for Percent Change of Daily Cornstarch Intake

Analysis	DTX401: LS mean	Placebo: LS mean	Difference (95% CI)
1. 4/7 Rule	-40.3	-9.1	-31.2 (-42.5, -19.5)
2. MI under MAR	-40.8	-10.7	-30.2 (-41.8, -18.6)
3. Tipping Point (Shift for DTX401+65%)	-31.2	-12.1	-19.1 (-38.3, 0.2)
4. Intercurrent Events*	-40.2	-10.9	-29.3 (-40.9, -17.7)
5. Use 4 weeks of data prior to visit	-40.9	-10.2	-30.7 (-42.1, -19.2)
6. Use Median CS intake	-34.7	-6.5	-28.2 (-29.9, -16.6)

* A total of 11 intercurrent events were reported in five patients (two in placebo group and three in DTX401 group).

Source: BLA 125858/0, Clinical Study Report-tfl, Tables 14.2.1.1.9 through 14.2.1.1.14, pp553-582.

6.1.11.2 Analyses of Secondary Endpoints

6.1.11.2.1 Total Daily Doses of Cornstarch (Subject to Multiplicity)

This key secondary endpoint evaluated the change from baseline to Week 48 in number of total daily doses of cornstarch (Table 11). The LS means (SE) were -0.2 (0.2) in the placebo group and -1.1 (0.2) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: -0.9 [0.3], $p = 0.0011$). Given the potential negative correlation among the endpoint, statistical significance was assessed using both the Hochberg and Holm methods, with significance achieved under either method.

Table 11 Number of Daily Doses of Cornstarch (mITT Population)

Visit	Placebo (N = 24)	DTX401 (N = 20)
Baseline		
n	24	20
Mean (SD)	5.1 (1.4)	5.8 (1.4)
Week 24		
n	24	20
Mean (SD)	4.8 (1.4)	5.0 (1.6)
Change from Baseline, Mean (SD)	-0.3 (0.7)	-0.9 (0.9)
Week 36		
n	22	19
Mean (SD)	5.0 (1.4)	4.7 (1.5)
Change from Baseline, Mean (SD)	0.0 (0.6)	-1.0 (0.7)
Week 48		
n	23	19
Mean (SD)	5.0 (1.3)	4.6 (1.7)
Change from Baseline, Mean (SD)	-0.1 (0.6)	-1.1 (0.9)
LS Mean (SE)	-0.2 (0.2)	-1.1 (0.2)
95% CI	(-0.6, 0.1)	(-1.5, -0.7)
LS Mean Difference (SE) [DTX401-Placebo]		-0.9 (0.3)
95% CI		(-1.4, -0.4)
p value		0.0011

LS=Least squares; mITT= Modified intent-to-treat; MMRM=Mixed model for repeated measures; SD=Standard deviation; SE=Standard error; NA=Not available.

Source: BLA 125858/0, Clinical Study Report, Table 10, p78.

The analysis results based on all-treated are presented in Table 12. The LS mean (SE) change from baseline to Week 48 in total daily dose of cornstarch intake was -0.2 (0.2) in the placebo group compared with -1.1 (0.2) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: -0.9 (0.3), $p = 0.0004$). The results based on the all-randomized and per-protocol populations were similar (not presented).

Table 12 Number of Daily Doses of Cornstarch (All-Treated Population)

Visit	Placebo (N = 25)	DTX401 (N = 21)
Baseline		
n	25	21
Mean (SD)	5.1 (1.4)	5.8 (1.3)
MMRM Estimates at Week 48		
LS Mean (SE)	-0.2 (0.2)	-1.1 (0.2)
LS Mean Difference [DTX401-Placebo] (95% CI):	-0.9 (-1.4, -0.4)	

CI=Confidence interval; LS=Least squares; MMRM=Mixed-model for repeated measures; SD=Standard deviation; SE=Standard error.

The LS Mean, LS Mean Difference, SE, 95% CI and 2-sided p-value are from MMRM (mixed-model for repeated measures) which includes percent change from baseline in daily cornstarch intake as the dependent variable, stratification factors, visit, treatment, and visit by treatment as fixed factors and adjusted for baseline measurement.

Source: Reviewer's summary and BLA 125858/0.42, Tables for Response to FDA Clinical Information Request Received on 20Jul2026, Table 14.2.1.2.1.1a, p1.

Reviewer's comment:

The applicant calculated the average number of doses per patient per visit by rounding to the nearest integer. I recalculated the MMRM results using the actual average number of doses without rounding. At Week 48, the LS mean changes from baseline to Week 48 are -1.2 and -0.2, with an LS mean difference (95% CI) of -1.0 (-1.4, -0.5); $p < 0.0001$.

Supplementary Analysis:

Number of Nighttime Cornstarch Doses

The results of nighttime dose frequency at Week 48 are presented in Table 13. Nighttime cornstarch dose frequency was defined as any cornstarch dose for which the patient reported having to wake from sleep to administer it. At Week 48, the nighttime dose of cornstarch change from baseline to Week 48 in the placebo group was 0.7 (0.3) doses and was -0.2 (0.3) doses in the DTX401 group. The LS mean difference (SE) [DTX401-Placebo] is -0.9 (0.4) with $p=0.0105$.

Table 13 Nighttime Dose Frequency (mITT Population)

Visit	Placebo	DTX401
Baseline		
n	15	15
Mean (SD)	1.7 (1.2)	1.7 (0.7)
Week 48		
n	14	14
Mean (SD)	2.1 (1.8)	1.2 (0.8)
Change from Baseline, Mean (SD)	0.5 (1.3)	-0.4 (0.6)
LS Mean (SE)	0.7 (0.3)	-0.2 (0.3)
95% CI	(0.2, 1.2)	(-0.8, 0.3)
LS Mean Difference (SE) [DTX401-Placebo]	-0.9 (0.4)	
95% CI	(-1.7, -0.2)	
p value	0.0105	

CI=Confidence interval; mITT=Modified intent-to-treat; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report, Table 11, p81.

Reviewer's comment:

The applicant's analysis above excluded all patients with a baseline nighttime dose of zero, which disrupted the randomization balance and undermined the basis for causal inference. Additionally, the approach of rounding the average number of doses misclassified a few patients who actually recorded nighttime doses over the average 4-week baseline period as non-nighttime users. We therefore performed an additional analysis including all treated patients and using the actual average number of nighttime doses without rounding, which was considered more appropriate for this analysis. As shown in Table 14, the LS mean changes from baseline to Week 48 are 0.5 in the placebo group and -0.1 in the DTX401 group, with an LS mean difference (95% CI) of -0.6 (-1.1, -0.3).

Table 14 Nighttime Dose Frequency Without Rounding (All-Treated Population)

Visit	Placebo	DTX401
Baseline		
n	25	21
Mean (SD)	1.1 (1.2)	1.2 (1.0)
Week 48		
n	23	19
LS Mean (SE)	0.5 (0.2)	-0.1 (0.2)
95% CI	(0.1, 0.8)	(-0.6, 0.3)
LS Mean Difference (95%CI) [DTX401-Placebo]	-0.6 (-1.1, -0.3)	

CI=Confidence interval; SD=Standard deviation; SE=Standard error.

Source: Reviewer's summary.

2. I performed additional descriptive analyses on nighttime cornstarch use status change (Table 15). Among the patients who required nighttime cornstarch at baseline, 1 of 18 patients in the placebo group and 2 of 17 patients in the DTX401 group were completely off nighttime cornstarch at Week 48. During the crossover period, 4 of 14 patients in the crossover placebo→DTX401 group were completely off nighttime cornstarch at Week 48 post DTX401 treatment and 3 patients in the DTX401 group were completely off nighttime cornstarch at Week 96.

Among the patients who did not take nighttime cornstarch at baseline, two of seven patients in the placebo group and three of four patients in the DTX401 resumed nighttime cornstarch intake at Week 48. During the crossover period, two of five patients in the crossover placebo→DTX401 group resumed nighttime cornstarch intake, and one patient in the DTX401 group required nighttime cornstarch at Week 96.

Because of the small sample size and unknown confounding, the observed findings are difficult to interpret.

Table 15 Nighttime Cornstarch Usage Analysis at Week 48 and Week 96 (All-Treated Population)

<i>Visit</i>	<i>Placebo (N=25)</i>	<i>DTX401 (N=21)</i>	<i>Crossover Placebo→DTX401^a (N=19)</i>
<i>Number of patients who received Nighttime Cornstarch at baseline</i>	<i>N=18</i>	<i>N=17</i>	<i>N=14</i>
<i>Number of patients who received nighttime Cornstarch at baseline but were completely off after baseline</i>			
<i>Week 48</i>	<i>1</i>	<i>2</i>	<i>4</i>
<i>Week 96</i>		<i>3</i>	<i>1</i>
<i>Number of patients who did not receive Nighttime Cornstarch at baseline</i>	<i>N=7</i>	<i>N=4</i>	<i>N=5</i>
<i>Number of patients who did not receive Nighttime Cornstarch but required Nighttime after baseline</i>			
<i>Week 48</i>	<i>2</i>	<i>3</i>	<i>2</i>
<i>Week 96</i>		<i>1</i>	<i>1</i>

^a This column includes results and statistics for the placebo group patients in the weeks after DTX401 treatment. Baseline for the crossover placebo→DTX401 group is the last observation prior to DTX401 dosing.

Source: Reviewer's summary.

6.1.11.2.2 Percentage of Glucose Values in Hypoglycemic Range (< 70 mg/dL) (Subject to Multiplicity)

The results of the change of percentage of Glucose Values in Hypoglycemic Range (<70 mg/dL) are presented in Table 16. At Week 48, the LS mean (SE) changes from baseline in percentage of glucose values < 70 mg/dL were 0.1% (0.9%) in the placebo group and 3.1% (1.0%) in the DTX401 group. The difference (95% CI) between the treatment groups was 3.1% (0.6%, 5.5%). This result met the non-inferiority with a margin of 10%. On the other hand, it would be statistically significant at 0.05 level against the favor of the DTX401 group, under the null hypothesis of no difference. I defer to the clinical review team regarding the clinical meaningfulness of this finding.

Table 16 Percent Time (%) in Range of Glucose Values < 70 mg/dL (mITT Population)

Visit	Placebo (N = 24)	DTX401 (N = 20)
Baseline		
n	24	20
Mean (SD)	2.0 (2.2)	2.5 (2.6)
Week 24		
n	24	19
Mean (SD)	2.1 (3.4)	3.8 (6.0)
Change from Baseline, Mean (SD)	0.1 (3.4)	1.4 (5.1)
Week 36		
n	23	19
Mean (SD),	1.8 (2.3)	3.7 (4.7)
Change from Baseline, Mean (SD)	-0.2 (2.2)	1.3 (3.9)
Week 48		
n	23	19
Mean (SD)	2.1 (1.9)	5.5 (6.5)
Change from Baseline, Mean (SD)	0.1 (2.6)	3.1 (5.2)
LS Mean (SE)	0.1 (0.9)	3.1 (1.0)
95% CI	(-1.6, 1.8)	(1.2, 5.0)
LS Mean Difference (SE) [DTX401-Placebo]		3.1 (1.2)
95% CI		(0.6, 5.5)

CI=Confidence interval; mITT=Modified intent-to-treat; LS=Least squares; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report, Table 13, p93.

The analysis based on all-treated population is presented in Table 17. The LS mean (SE) change from baseline to Week 48 in percentage of glucose values < 70 mg/dL was 0.1% (0.8%) in the placebo group compared with 3.1% (0.8%) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: 3.1% [1.1%]). Similar results were observed using the all-randomized and per-protocol populations, as well as sensitivity analyses (not presented).

Table 17 Percent Time (%) in Range of Glucose Values < 70 mg/dL (All-Treated Population)

Visit	Placebo (N = 25)	DTX401 (N = 21)
Baseline		
n	25	21
Mean (SD)	1.9 (2.2)	2.5 (2.5)
MMRM Estimates at Week 48		
LS Mean (SE)	0.1 (0.8)	3.1 (0.8)
LS Mean Difference [DTX401-Placebo] (95% CI):	3.1 (0.9, 5.2)	

CI=Confidence interval; LS=Least squares; MMRM=Mixed-model for repeated measures; SD=Standard deviation; SE=Standard error.

The LS Mean, LS Mean Difference, SE, 95% CI and 2-sided p-value are from MMRM (mixed-model for repeated measures) which includes percent change from baseline in daily cornstarch intake as the dependent variable, stratification factors, visit, treatment, and visit by treatment as fixed factors and adjusted for baseline measurement.

Source: BLA 125858/0.42, Tables for Response to FDA Clinical Information Request Received on 20Jul2026, Table 14.2.1.3.1.1a, p12.

Reviewer's comment:

SMBG data collected during the 1 week prior to the visit were evaluated to assess the consistency of the findings derived from CGM data. CDRH was consulted regarding the adequacy of the CGM device performance and the use of CGM-derived data in this study. Taking into consideration the limited amount of available SMBG data and the known limitations in CGM measurement accuracy, CDRH considered the CGM-derived data acceptable for the interpretation and evaluation of the study results.

Supplementary Analysis:

The percentage of glucose values in severe hypoglycemic range (< 54 mg/dL) and the percentage of glucose values in severe hypoglycemic range (> 120 mg/dL) are presented in Table 18. At Week 48, the LS mean (SE) changes from baseline in percentage of glucose values < 54 mg/dL were 0.2% (0.2%) in the placebo group and 0.7% (0.3%) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: 0.5% [0.3%]; 95% CI [-0.2%, 1.2%]). At Week 48, the LS mean (SE) changes from Baseline in percentage of glucose values > 120 mg/dL were 6.5% (3.1%) in the placebo group and -2.8% (3.4%) in the DTX401 group (LS mean difference [SE][DTX401-Placebo]: -9.2% [4.4%]; 95% CI [-17.9%, -0.5%]). Similar results were observed using the all-treated population (not presented).

Table 18 Percent Time (%) in Range of Glucose Values < 54 mg/dL and > 120 mg/dL (mITT Population)

	< 54 mg/dL: Placebo (N=24)	< 54 mg/dL: DTX401 (N=20)	> 120 mg/dL: Placebo (N=24)	> 120 mg/dL: DTX401 (N=20)
Baseline				
n	24	20	24	20
Mean (SD)	0.2 (0.4)	0.3 (0.5)	36.8 (18.2)	34.2 (17.8)
Week 48				
n	23	19	23	19
Mean (SD)	0.5 (0.7)	1.1 (1.5)	42.8 (14.3)	34.0 (19.0)
Change from Baseline, Mean (SD)	0.2 (0.7)	0.8 (1.2)	6.4 (21.4)	-0.2 (18.8)
LS Mean (SE)	0.2 (0.2)	0.7 (0.3)	6.5 (3.1)	-2.8 (3.4)
95% CI	(-0.2, 0.7)	(0.2, 1.3)	(0.4, 12.5)	(-9.5, 4.0)
LS Mean Difference (SE) [DTX401-Placebo]	0.5 (0.3)		-9.2 (4.4)	
95% CI	(-0.2, 1.2)		(-17.9, -0.5)	

CI=Confidence interval; LS=Least square; mITT=Modified Intent-to-treat; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report, Table 15, p101 and BLA 125858/0, Clinical Study Report-tfl, Table 14.2.1.3.2.1.2, p1386, Table 14.2.1.8, p2330.

6.1.11.2.5 Percentage of Glucose Values in 70 – 120 mg/dL Range (Not Subject to Multiplicity)

The results of the change of percentage of Glucose Values in 70 – 120 mg/dL are presented in Table 19. At Week 48, the LS mean (SE) changes from baseline in percentage of glucose values in the 70 – 120 mg/dL range were -6.5% (2.6%) in the placebo group and -0.5% (2.9%) in the DTX401 group, resulting a LS mean difference [SE] [DTX401-Placebo] of 6.0% [3.8%]; 95% CI: [-1.5%, 13.5%].

Table 19 Percent Time (%) in Range of Glucose Values 70-120 mg/dL (mITT Population)

Weeks After Treatment	Placebo (N = 24)	DTX401 (N = 20)
Baseline		
n	24	20
Mean (SD)	61.2 (17.0)	63.4 (16.2)
Week 48		
n	23	19
Mean (SD)	55.1 (13.9)	60.5 (14.3)
Change from Baseline, Mean (SD)	-6.5 (20.2)	-2.9 (16.8)
LS Mean (SE)	-6.5 (2.6)	-0.5 (2.9)
95% CI	(-11.8, -1.3)	(-6.3, 5.3)
LS Mean Difference (SE) [DTX401-Placebo]	6.0 (3.8)	
95% CI	(-1.5, 13.5)	

CI=Confidence Interval; LS=Least squares; mITT=Modified intent-to-treat; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report, Table 16, p104.

The analysis based on all-treated population is presented in Table 20. The LS mean (SE) change from baseline to Week 48 in percentage of glucose values 70-120 mg/dL was -6.7% (2.5%) in the placebo group compared with -1.0% (2.8%) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: 5.7% [3.7%]).

Table 20 Percent Time (%) in Range of Glucose Values 70-120 mg/dL (All-Treated Population)

Visit	Placebo (N = 25)	DTX401 (N = 21)
Baseline		
n	25	21
Mean (SD)	60.4 (17.0)	63.7 (15.9)
MMRM Estimates at Week 48		
LS Mean (SE)	-6.7 (2.5)	-1.0 (2.8)
LS Mean Difference [DTX401-Placebo] (95% CI):	5.7 (-1.5, 13.0)	

CI=Confidence interval; LS=Least squares; MMRM=Mixed-model for repeated measures; SD=Standard deviation; SE=Standard error.

The LS Mean, LS Mean Difference, SE, 95% CI and 2-sided p-value are from MMRM (mixed-model for repeated measures) which includes percent change from baseline in daily cornstarch intake as the dependent variable, stratification factors, visit, treatment, and visit by treatment as fixed factors and adjusted for baseline measurement.

Source: Reviewer's summary.

6.1.11.2.6 Time to Hypoglycemia During Controlled Fasting Challenge (Not Subject to Multiplicity)

The results for TTH during CFC are presented in Table 21. At Week 48, the LS mean (SE) change from baseline in TTH during the CFC was 0.5 (0.8) hours in the placebo group and 1.1 (0.9) hours in the DTX401 group (LS mean difference [SE] [DTX401-

Placebo]: 0.6 [1.1] hours; 95% CI: [-1.7, 2.9] hours). The results did not show statistically significant difference between the two groups.

Table 21 Time to Hypoglycemia (hours) during Controlled Fasting Challenge at Week 48 (mITT Population)

Weeks After Treatment	Placebo	DTX401
Baseline		
n	24	20
Mean (SD)	6.2 (3.1)	7.1 (4.1)
Week 36		
n	20	16
Mean (SD)	7.2 (3.8)	9.6 (5.1)
Change from Baseline, Mean (SD)	0.7 (2.9)	1.8 (4.0)
Week 48		
n	23	18
Mean (SD)	7.0 (3.7)	8.3 (4.9)
Change from Baseline, Mean (SD)	0.7 (2.7)	1.0 (4.7)
LS Mean (SE)	0.5 (0.8)	1.1 (0.9)
95% CI	(-1.1, 2.1)	(-0.7, 3.0)
LS Mean Difference (SE) [DTX401-Placebo]	0.6 (1.1)	
95% CI	(-1.7, 2.9)	
p value	0.590	

CI=Confidence interval; mITT=Modified intent-to-treat; LS=Least squares; SD=Standard deviation; SE=Standard error.

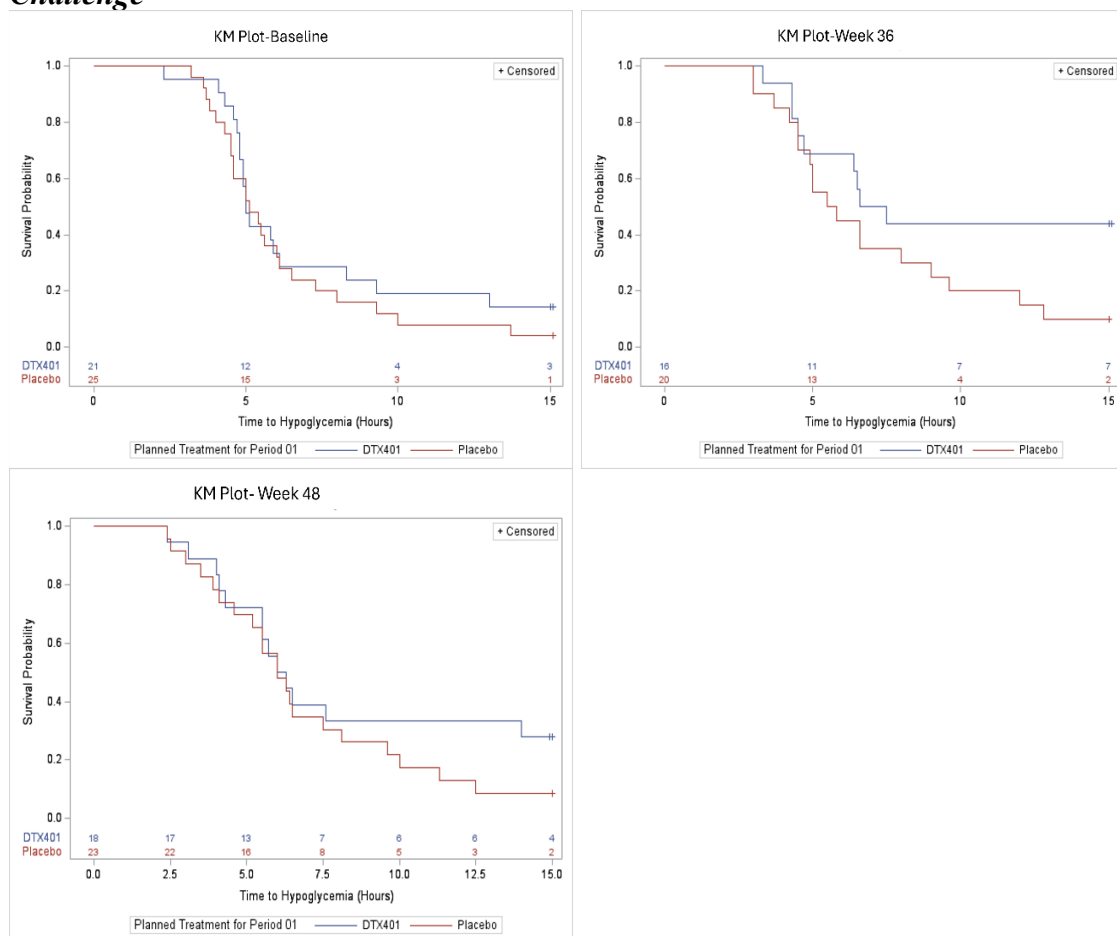
Source: BLA 125858/0, Clinical Study Report-tfl, Table 14.2.1.6.1.1, p1898.

The stopping criteria of CFC included: 1) the patients' glucose level decreases to < 54 mg/dL (< 3.0 mmol/L); 2) the patients experience signs and symptoms of hypoglycemia; 3) when the fast reaches 15 hours without hypoglycemia, whichever occurred first. The stop time of the CFC would be recorded in the electronic case report form (eCRF).

Reviewer's comment:

A limitation of the MMRM analysis is that patients who did not experience hypoglycemia during the 15-hour CFC procedure were assigned an event time of 15 hours. This approach may distort the true distribution of the endpoint and will introduce bias when using the MMRM model. Because this endpoint is inherently subject to right censoring, non-parametric methods or survival analysis are more appropriate. I conducted a Kaplan-Meier analysis of TTH each visit week (Figure 3). There was slight numerical improvement of TTH in DTX401 group than Placebo group at Week 36 and Week 48. The log rank p-values for Baseline, Week 36 and Week 48 were 0.3942, 0.0762, and 0.2553, respectively. No definitive conclusion can be drawn regarding the treatment effect.

Figure 3 Kaplan-Meier Plot for Time to Hypoglycemia during Controlled Fasting Challenge



KM= Kaplan-Meier

Source: Reviewer's analysis.

Supplementary Analysis:

Time between a glucose level of 70 mg/dL to < 54 mg/dL during the CFC

The results of the time taken from a glucose level of 70 mg/dL to <54 mg/dL during CFC is presented in Table 22. At Week 48, the changes from baseline of the drop in glucose levels from 70 mg/dL to < 54 mg/dL during the CFC were 7.9 (24.5) min in the placebo group and 32.3 (25.8) min in the DTX401 group (the LS Mean Difference [SE] [DTX401-Placebo]: 24.4 [34.2] min; 95% CI: [-44.3, 93.1] min).

Table 22 Time Taken from a Glucose Level of 70 mg/dL to <54 mg/dL (minutes) During the Controlled Fasting Challenge (mITT Population)

Weeks After Treatment	Placebo	DTX401
Baseline		
n	20	19
Mean (SD)	105.6 (88.2)	90.0 (72.0)
Week 36		
n	16	13
Mean (SD)	126.6 (103.2)	122.8 (69.2)
Change from Baseline, Mean (SD)	12.6 (102.8)	22.6 (66.0)
Week 48		
n	17	16
Mean (SD)	108.3 (115.8)	131.4 (120.0)
Change from Baseline, Mean (SD)	1.6 (151.7)	38.2 (61.3)
LS Mean (SE)	7.9 (24.5)	32.3 (25.8)
95% CI	(-41.3, 57.2)	(-19.4, 84.1)
LS Mean Difference (SE) [DTX401-Placebo]	24.4 (34.2)	
95% CI	(-44.3, 93.1)	
p value	0.479	

CI=Confidence interval; LS=Least squares; mITT=Modified intent-to-treat; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report-tfl, Table 14.2.3.9.1, p3496.

6.1.11.2.3 Patient Global Impression of Change (PGIC) (Subject to Multiplicity)

The results for PGIC at Week 48 are presented in Table 23. No significant difference was observed between treatment groups at Week 48 (LS mean [SE] Placebo = 1.0 [0.3] vs DTX401 = 1.4 [0.3]; MMRM p = 0.318; Wilcoxon Rank Sum Test, p = 0.131).

Table 23 PGIC (mITT Population)

	Placebo (N = 24)	DTX401 (N = 20)
Week 48		
n	23	19
Mean (SD)	1.0 (1.1)	1.4 (1.4)
Median	1	2
MMRM Estimates		
LS Mean (SE)	1.0 (0.3)	1.4 (0.3)
95% CI	(0.4, 1.5)	(0.7, 2.0)
LS Mean Difference (SE) [DTX401-Placebo]	0.4 (0.4)	
95% CI	(-0.4, 1.2)	
p-value	0.318	
Change in GSDIa Since Start of Study, n (%)		
Much improved	2 (8.7)	5 (26.3)
Moderately improved	6 (26.1)	5 (26.3)
Minimally improved	4 (17.4)	5 (26.3)
No change	11 (47.8)	2 (10.5)
Minimally worse	0 (0.0)	1 (5.3)
Moderately worse	0 (0.0)	1 (5.3)
Much worse	0 (0.0)	0 (0.0)

CI=Confidence interval; mITT=Modified intent-to-treat; LS=Least squares; SD=Standard deviation; SE=Standard error.

Source: BLA 125858/0, Clinical Study Report, Table 22, p121.

The analysis based on all-treated population is presented in Table 24. At Week 48, The LS mean (95% CI) difference (DTX401-Placebo) between the placebo group and the DTX401 group was 0.4 (-0.4, 1.2), p=0.2781.

Table 24 PGIC (All Treated Population)

MMRM Estimates at Week 48	Placebo (N = 25)	DTX401 (N = 21)
LS Mean (SE)	1.0 (0.3)	1.4 (0.3)
LS Mean Difference [DTX401-Placebo] (95% CI):	0.4 (-0.4, 1.2)	

CI=Confidence interval; LS=Least squares; MMRM=Mixed-model for repeated measures; SE=Standard error.

The LS Mean, LS Mean Difference, SE, 95% CI and 2-sided p-value are from MMRM (mixed-model for repeated measures) which includes percent change from baseline in daily cornstarch intake as the dependent variable, stratification factors, visit, treatment, and visit by treatment as fixed factors and adjusted for baseline measurement.

Source: BLA 125858/0.42, Tables for Response to FDA Clinical Information Request Received on 20Jul2026, Table 14.2.1.4.1.1a, p23.

6.1.11.3 Subpopulation Analyses

Subgroup analyses are presented in Table 25. The analysis results within each subgroup were generally consistent across subgroups and were consistent with the primary analysis.

Table 25 Subgroup Analysis for Age, Sex, Race and Ethnicity (All-Treated Population)

Subgroup (N: DTX401 vs Placebo)	LS Mean Difference (95% CI): %CFB* Daily Dose Intake;	LS Mean Difference (95% CI): CFB Number of Daily Dose	LS Mean Difference (95% CI): CFB Percentage of Glucose Values < 70 mg/dL
Age			
8 – 17 years (N: 10 vs 10)	-31.7 (-45.8, -17.5)	-0.8 (-1.3, -0.2)	4.2 (0.2, 8.2)
≥ 18 years (N: 11 vs 15)	-33.1 (-47.1, -19.2)	-1.0 (-1.7, -0.3)	1.66 (-0.4, 3.7)
Sex			
Female (N: 7 vs 12)	-29.4 (-51.9, -6.9)	-0.9 (-1.6, -0.2)	1.4 (-3.5, 6.3)
Male (N: 14 vs 13)	-32.1 (-42.3, -22.0)	-0.8 (-1.6, -0.1)	4.1 (1.9, 6.3)
Ethnicity			
Hispanic or Latino (N: 3 vs 3)	-16.3 (-34.0, 1.4)	-0.2 (-1.0, 0.7)	-0.6 (-3.2, 2.0)
Not Hispanic or Latino (N: 16 vs 17)	-35.5 (-48.6, -22.4)	-1.1 (-1.7, -0.5)	4.1 (1.1, 7.1)
Not Reported (N: 2 vs 5)	-19.9 (-35.4, -4.4)	-1.3 (-1.8, -0.8)	1.3 (-1.3, 3.9)
Race			
White (N: 18 vs 23)	-33.2 (-43.9, -22.6)	-0.9 (-1.5, -0.4)	3.6 (1.2, 6.0)
Not White (N: 3 vs 2) ^{1,3}	NA	NA	NA
Percentage of values in the glucose range at Baseline			
< 60% (N: 5 vs 5)	-30.5 (-49.2, -11.9)	-0.3 (-1.3, 0.7)	1.2 (-1.5, 3.9)
≥ 60% and ≤ 85% (N: 13 vs 15)	-33.0 (-44.6, -21.5)	-1.1 (-1.7, -0.4)	2.8 (-0.1, 5.8)
> 85% (N: 3 vs 5)	-28.7 (-90.4, 32.9)	-1.2 (-3.1, 0.6)	13.9 (7.5, 20.3)
Pubertal stage status at Baseline			
1, 2 or 3 (N: 7 vs 3)	-8.1 (-64.8, 48.5)	-1.0 (-1.5, -0.5)	1.4 (-3.8, 6.7)
4 or 5 (N: 3 vs 6)	-43.8 (-75.3, -12.2)	-0.6 (-2.0, 0.8)	3.8 (-4.1, 11.7)
Geographical Region			
North America (N: 13 vs 17)	-29.9 (-43.9, -15.9)	-0.4 (-1.1, 0.2)	4.6 (1.4, 7.8)
Europe (N: 6 vs 6)	-32.9 (-43.2, -22.7)	-1.9 (-2.9, -0.9)	0.9 (-2.0, 3.7)
Brazil (N: 2 vs 2) ¹	NA	NA	NA
AAV8 Antibodies at Baseline			
Yes (N: 1 vs 1) ¹	NA	NA	NA
No (N: 20 vs 24)	-31.3 (-41.7, -20.8)	-0.9 (-1.4, -0.4)	3.1 (0.9, 5.3)
Average Number of Total Doses of Cornstarch at Baseline²			
< 4 doses (N: 1 vs 3) ¹	NA	-	-
≥ 4 doses (N: 20 vs 22)	-30.1 (-40.7, -19.4)	-	-
Using Glycosade (Yes/No) at Baseline²			

Subgroup (N: DTX401 vs Placebo)	LS Mean Difference (95% CI): %CFB* Daily Dose Intake;	LS Mean Difference (95% CI): CFB Number of Daily Dose	LS Mean Difference (95% CI): CFB Percentage of Glucose Values < 70 mg/dL
Yes (N: 10 vs 11)	-36.4 (-48.6, -24.2)	-	-
No (N: 11 vs 14)	-27.3 (-43.6, -10.9)	-	-

CI=Confidence interval; LS=Least squares; CFB=Change from Baseline.

N: Number of patients in each subgroup.

¹ Due to limited sample size (n<5), subgroup analysis are not performed.

² Based on the statistical analysis plan, the baseline subgroups defined by the average total number of cornstarch doses and Glycosade use (Yes/No) were not applied to the endpoints of number of daily doses or percentage of glucose values <70 mg/dL.

³ Not white includes Asian and Not Reported or Unknown Race.

Source: Reviewer's summary and Adapted from BLA 125858/0.42, Tables for Response to FDA Clinical Information Request Received on 20Jul2026, Table 14.2.1.1.5.2.1a through Table 14.2.1.4.1.1.4c, pp30-387.

6.1.11.4 Dropouts and/or Discontinuations

Of the 49 randomized patients, 3 patients discontinued prior to receiving blinded IP. Of the 46 dosed patients, two dosed patients dropped out and did not provide any post-dosing assessment. Sensitivity analyses have shown that the impact of dropouts and missing data on the study results was minimal, and the conclusions for the primary and key secondary endpoint remained unchanged.

6.1.11.5 Exploratory and Post Hoc Analyses

Crossover period results are shown in the following subsections for the primary and key secondary endpoints. During crossover period, data at Weeks 72, 78, 84, 90, and 96 would be included in the model for the crossover DTX401 group. The model would include the treatment group (DTX401 and crossover DTX401), average cornstarch intake at baseline, stratification factors, study visit, and interaction of visit by treatment as covariates. To calculate the change from baseline, baseline would be defined as Week 48 visit for crossover DTX401 group and Day 0 visit for DTX401 group. These analyses are presented in descriptive manner. Because not all randomized subjects continued during the crossover period, a causal inference on treatment effect cannot be made.

6.1.11.5.1 Daily Cornstarch Intake

The percent change of daily cornstarch intake from baseline during crossover period is presented in Table 26. At 48 weeks after DTX401 treatment (i.e., Week 96) for the Crossover Placebo→DTX401 group, the mean (SD) percent change from Crossover Baseline in total daily cornstarch intake was -61.3% (26.8%). At Week 96, the mean (SD) percent change from Baseline in total daily cornstarch intake was -60.8% (19.7%) in the DTX401 group.

Table 26 Daily Cornstarch Intake During Crossover (mITT Population)

Baseline (g)	Placebo	DTX401	Crossover Placebo→DTX401^a
n	24	20	19
Mean (SD)	268.4 (110.0)	294.1 (85.3)	232.5 (112.8)
Week 48			
n	23	19	18
Mean (SD)	239.1 (112.0)	171.1 (70.9)	84.2 (60.6)
Change from Baseline, Mean (SD)	-10.1 (18.0)	-40.9 (18.4)	-61.3 (26.8)
Week 96			
n	-	15	2
Mean (SD)	-	101.2 (46.3)	133.0 (11.3)
Change from Baseline, Mean (SD)	-	-60.8 (19.7)	-56.7 (1.7)

^a This column includes results and statistics for the placebo group patients in the weeks after DTX401 treatment. Baseline for the crossover placebo→DTX401 group is the last observation prior to DTX401 dosing.

mITT=Modified intention-to-treat; SD=Standard deviation.

Source: BLA 125858/0, Clinical Study Report, Table 8, p69.

6.1.11.5.2 Total Daily Doses of Cornstarch

The change of number of total daily doses of cornstarch from baseline during crossover is presented in Table 27. At 48 weeks after treatment with DTX401 for the crossover placebo→DTX401 group, the mean (SD) change from crossover baseline in number of total daily doses of cornstarch was -1.6 (1.9). At Week 96, the mean (SD) change from baseline in number of total daily doses of cornstarch was -1.9 (1.5) in the DTX401 group.

Table 27 Number of Daily Doses of Cornstarch During Crossover (mITT Population)

	Placebo	DTX401	Crossover Placebo→DTX401 ^a
Baseline			
n	25	21	19
Mean (SD)	5.2 (1.4)	5.8 (1.4)	4.8 (1.6)
Week 48			
n	23	19	18
Mean (SD)	4.9 (1.5)	4.6 (1.7)	3.3 (2.4)
Change from Baseline, Mean (SD)	-0.1 (0.6)	-1.1 (0.9)	-1.6 (1.9)
Week 96			
n	-	15	2
Mean (SD)	-	3.5 (1.4)	3.5 (0.7)
Change from Baseline, Mean (SD)	-	-1.9 (1.5)	-2.0 (0.0)

^a This column includes results and statistics for the placebo group patients in the weeks after DTX401 treatment. Baseline for the crossover placebo→DTX401 group is the last observation prior to DTX401 dosing.

mITT=Modified intention-to-treat; SD=Standard deviation.

Source: BLA 125858/0, Clinical Study Report, Table 10, p78.

6.1.11.5.3 Percentage of Glucose Values in Hypoglycemic Range (< 70 mg/dL)

The results of percentage of glucose values in hypoglycemic range (< 70 mg/dL) during crossover period are presented in Table 28. At 48 weeks after treatment with DTX401, the mean (SD) increase from crossover baseline in percentage of glucose values in the hypoglycemic range (< 70 mg/dL) was 2.4% (3.4%) in the crossover placebo→DTX401 group. At Week 96, the mean (SD) change from baseline in percentage of glucose values in the hypoglycemic range (< 70 mg/dL) as assessed by CGM was 5.2% (6.3%) in the DTX401 group.

Table 28 Percent Time (%) in Range of Glucose Values < 70 mg/dL During Crossover Period (mITT Population)

	Placebo	DTX401	Crossover Placebo →DTX401 ^a
Baseline			
n	24	20	19
Mean (SD)	2.0 (2.2)	2.5 (2.6)	1.8 (1.6)
Week 48			
n	23	19	19
Mean (SD)	2.1 (1.9)	5.5 (6.5)	4.3 (3.9)
Change from Baseline, Mean (SD)	0.1 (2.6)	3.1 (5.2)	2.4 (3.4)
Week 96			
n		19	2
Mean (SD)		7.6 (7.00)	2.5 (3.0)
Change from Baseline, Mean (SD)		5.2 (6.3)	-0.5 (0.6)

^a This column includes results and statistics for the Placebo group patients in the weeks after DTX401 treatment. Baseline for the Crossover Placebo→DTX401 group is the last observation prior to DTX401 dosing.

mITT=Modified intention-to-treat; SD=Standard deviation.

Source: BLA 125858/0, Clinical Study Report, Table 13, p93.

6.1.11.5.4 PGIC

The results for PGIC during crossover period are presented in Table 29. At 48 weeks after treatment for the crossover placebo→DTX401 group, the mean (SD) PGIC score was 2.1 (1.0) (median was 2.0). For the DTX401 group at Week 96, the mean (SD) PGIC score was 1.4 (1.2) (median = 1.0).

Table 29 PGIC (mITT Population)

	Placebo (N = 24)	DTX401 (N = 20)	Crossover Placebo→DTX401 ^a (N=19)
Week 48			
n	23	19	19
Mean (SD)	1.0 (1.1)	1.4 (1.4)	2.1 (1.0)
Median	1	2	2
Change in GSDIa Since Start of Study, n (%)			
Much improved	2 (8.7)	5 (26.3)	9 (47.4)
Moderately improved	6 (26.1)	5 (26.3)	4 (21.1)
Minimally improved	4 (17.4)	5 (26.3)	5 (26.3)
No change	11 (47.8)	2 (10.5)	1 (5.3)
Minimally worse	0 (0.0)	1 (5.3)	0 (0.0)
Moderately worse	0 (0.0)	1 (5.3)	0 (0.0)
Much worse	0 (0.0)	0 (0.0)	0 (0.0)
Week 96			
n		12	2
Mean (SD)		1.4 (1.2)	2.5 (0.7)
Median		1	2.5
Change in GSDIa Since Start of Study, n (%)			
Much improved		3 (25.0)	1 (50.0)
Moderately improved		2 (16.7)	1 (50.0)
Minimally improved		5 (41.7)	0 (0.0)
No change		1 (8.3)	0 (0.0)
Minimally worse		1 (8.3)	0 (0.0)
Moderately worse		0 (0.0)	0 (0.0)
Much worse		0 (0.0)	0 (0.0)

^a This column includes results and statistics for the Placebo group patients in the weeks after DTX401 treatment. Baseline for the Crossover Placebo→DTX401 group is the last observation prior to DTX401 dosing.

CI=Confidence interval; mITT=Modified intention-to-treat; LS=Least squares; SD=Standard deviation; SE=Standard error; PGIC= Patient Global Impression of Change.

Source: BLA 125858/0, Clinical Study Report, Table 22, p121.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No patients died during the study.

6.1.12.4 Nonfatal Serious Adverse Events

During PEAP, serious treatment-emergent adverse events (TEAEs) were reported in three patients in the Placebo group and eight patients in the DTX401 group. Twelve serious

TEAEs were reported in 9 patients (47.4%) in the Crossover Placebo→DTX401 group after DTX401 treatment, and a total of 25 serious TEAEs in 12 patients were reported in the DTX401 group during crossover period and follow-up period. Please refer to clinical review memo for serious TEAT reports.

6.1.12.5 Adverse Events of Special Interest (AESI)

The Applicant specified AESI of vector-induced hepatic effects, infusion-related reactions (IRRs), adrenal insufficiency, dorsal root ganglion (DRG) and peripheral nerve effects and AAV gene therapy class effects. Please refer to clinical review memo for the AESI reports.

6.1.12.7 Dropouts and/or Discontinuations

Two patients from the DTX401 group experienced one event each of IRR during the administration of DTX401. Both events were serious and Grade 3 in severity and resulted in immediate discontinuation of the infusion (one patient continued study with safety follow-up only; the other patient had incomplete efficacy results during PEAP). One patient from the placebo group was withdrawn from the study by the investigator after the PEAP due to elevation of liver enzymes. The patient did not meet criteria to crossover and receive DTX401 treatment at Week 48 due to increased aminotransferases.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This is an original BLA for an AAV8 based gene therapy GENGLYCOS, which is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years and older with glycogen storage disease type Ia (GSDIa).

The clinical studies in this submission consist of three studies: the pivotal study DTX401-CL301, the Phase 1/2 study 401GSDIA01 and the long-term follow-up study 401GSDIA02. The primary efficacy and safety evaluations were based on pivotal study DTX401-CL301.

Study Design of DTX401-CL301:

DTX401-CL301 is an ongoing a Phase 3 multicenter, randomized, double-blind, placebo-controlled study where a total of 49 patients were randomized in a 1:1 ratio to receive a single intravenous infusion of either GENGLYCOS at a dose of 1.0×10^{13} gc/kg body weight or placebo. Three patients discontinued prior to receiving any treatment and 46 patients received the assigned treatment. Study DTX401-CL301 comprised a 48-week, double-blind, placebo-controlled primary efficacy analysis period (PEAP; Day 1-Week 48), a 48-week, double-blind crossover period (Week 48-Week 96), and a 48-week follow-up period (Week 96-Week 144), for a total duration of 144 weeks.

Demographics:

Among 46 patients treated, the mean age was 20.5 years (range 8 to 37 years), 27 (58.7%) patients were male, 41 (89.1%) patients were White, 2 (4.3%) patients were

Asian, 3 (6.5%) patients were of unknown race or did not report race, and 6 (13.0%) patients were Hispanic or Latino.

Efficacy Results:

All 46 treated patients were included for efficacy evaluation. The primary efficacy endpoint was the percent change from baseline to Week 48 in daily cornstarch intake. The LS means (SE) of percent change from baseline to Week 48 were -10.2% (3.6%) in the placebo group and -41.1% (3.9%) in the DTX401 group, resulting in a statistically significant LS mean difference (95% CI) of -30.9% (-40.8%, -20.9%) [$p < 0.0001$]. This result met the prespecified superiority criterion for the primary endpoint.

There were three secondary endpoints subject to multiplicity control. For the secondary endpoint of the number of daily CS doses, the LS mean changes from baseline to Week 48 were -1.2 in the DTX401 group and -0.2 in the placebo group (LS mean difference [95% CI]: -1.0 [-1.4, -0.5] doses; $p < 0.0001$), reaching statistical significance. However, for the secondary endpoint of percent of glucose values in the hypoglycemic range (<70 mg/dL), a greater increase in the LS mean changes from baseline to Week 48 was observed in the DTX401 group (3.1%) compared to the placebo group (0.1%), resulting in an LS mean difference (95% CI) of 3.1% (0.9%, 5.2%), indicating a worse treatment response for DTX401 relative to placebo. Although this finding fell within the pre-specified non-inferiority margin of 10%, the FDA clinical review team determined during the review that this margin was not clinically justifiable, and an appropriate margin for this endpoint could not be established at the time of pre-specification.

There was no statistically significant difference between the two treatment groups in the PGIC.

Finally, the findings were inconclusive for time to hypoglycemia during the controlled fasting challenge, a protocol-defined exploratory secondary endpoint of particular clinical interest.

Safety Results:

During PEAP, 4 serious TEAEs were reported in 3 (3/25; 12.0%) patients in the placebo group and 10 serious TEAEs were reported in 8 (8/21; 38.1%) patients in the DTX401 group. Twelve serious TEAEs were reported in 9 patients (9/19; 47.4%) in the Crossover Placebo→DTX401 group after DTX401 treatment, and a total of 25 serious TEAEs in 12 (12/21; 57.1%) patients were reported in the DTX401 group during crossover period and follow-up period. No deaths occurred during the study.

10.2 Conclusions and Recommendations

Collectively, while DTX401 demonstrates a reduction in cornstarch CS intake, it is also associated with a slight increase in the risk of hypoglycemia. The clinical effectiveness remains highly uncertain and, given the totality of evidence, the benefit-risk profile is difficult to characterize. Nevertheless, in the context of a rare disease with limited therapeutic options and a significant unmet medical need, accelerated approval may be appropriate, with a post-marketing requirement to verify clinical benefit through a confirmatory trial.