

## BLA Clinical/Clinical Pharmacology Review and Evaluation

**Disclaimer:** In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

|                                            |                                                                                                                                                                                                         |
|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                    | Biologics Licensing Application, Original                                                                                                                                                               |
| <b>Application Number(s)</b>               | 125858                                                                                                                                                                                                  |
| <b>Priority or Standard</b>                | Priority Review                                                                                                                                                                                         |
| <b>Submission Date</b>                     | December 23, 2025                                                                                                                                                                                       |
| <b>PDUFA Goal Date</b>                     | August 23, 2026                                                                                                                                                                                         |
| <b>Division/Office</b>                     | Division of Clinical Evaluation General Medicine   Office of Clinical Evaluation   Office of Therapeutic Products   CBER                                                                                |
| <b>Review Completion Date</b>              | August 19, 2026                                                                                                                                                                                         |
| <b>Established Name</b>                    | Pariglasgene breCAPARVovec - opnr                                                                                                                                                                       |
| <b>Trade Name</b>                          | GENGLYCOS                                                                                                                                                                                               |
| <b>Pharmacologic Class</b>                 | Adeno-associated virus serotype 8 (AAV8)-based gene therapy                                                                                                                                             |
| <b>Code name</b>                           | DTX401                                                                                                                                                                                                  |
| <b>Applicant</b>                           | Ultragenyx Pharmaceutical Inc.                                                                                                                                                                          |
| <b>Formulation(s)</b>                      | A suspension for intravenous infusion with a concentration of $3.0 \times 10^{13}$ gc/mL. Each vial contains 2 mL of extractable volume.                                                                |
| <b>Dosing Regimen</b>                      | Single intravenous infusion of $1.0 \times 10^{13}$ genome copies per kilogram (GC/kg)                                                                                                                  |
| <b>Applicant Proposed Indication</b>       | (b) (4)                                                                                                                                                                                                 |
| <b>Recommendation on Regulatory Action</b> | Accelerated Approval                                                                                                                                                                                    |
| <b>Recommended Indication</b>              | GENGLYCOS is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adult and pediatric patients 8 years of age and older with glycogen storage disease type Ia (GSDIa) |

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## Glossary

|          |                                                 |
|----------|-------------------------------------------------|
| AAV8     | adeno-associated virus serotype 8               |
| ACTH     | adrenocorticotrophic hormone                    |
| ADA      | anti-drug-antibody                              |
| ADME     | absorption, distribution, metabolism, excretion |
| ADR      | adverse drug reaction                           |
| AE       | adverse event                                   |
| ALP      | alkaline phosphatase                            |
| ALT      | alanine aminotransferase                        |
| AST      | aspartate aminotransferase                      |
| AUC      | Area Under the Curve                            |
| BCC      | basal cell carcinoma                            |
| BL       | Baseline                                        |
| BLA      | Biologics License Application                   |
| BLOD     | below limit of detection                        |
| BLOQ     | below limit of quantification                   |
| BMI      | body mass index                                 |
| CFB      | change from Baseline                            |
| CFC      | controlled fasting challenge                    |
| CFR      | Code of Federal Regulations                     |
| CGM      | continuous glucose monitor(ing)                 |
| ClinRO   | clinician reported outcome                      |
| CMC      | chemistry, manufacturing, and controls          |
| COA      | clinical outcome assessment                     |
| coG6PC   | codon-optimized glucose-6-phosphatase           |
| COVID-19 | coronavirus disease 2019                        |
| CRF      | case report form                                |
| CSR      | Clinical Study Report                           |
| CTCAE    | Common Terminology Criteria for Adverse Event   |
| ddPCR    | Droplet Digital polymerase chain reaction       |
| DLT      | dose-limiting toxicity                          |
| DMF      | Drug Master File                                |
| DMP      | Disease Monitoring Program                      |
| DRG      | dorsal root ganglion                            |
| DS       | Day of Study                                    |
| ECG      | electrocardiogram                               |
| eCTD     | electronic common technical document            |
| EDC      | electronic data capture                         |
| EFD      | Embryo-fetal Developmental                      |
| eGFR     | estimated glomerular filtration rate            |
| ELISpot  | enzyme-linked immunosorbent spot assay          |
| EL-PFDD  | Externally led Patient-focused Drug Development |
| EOP2     | End-of-Phase 2                                  |
| FDA      | Food and Drug Administration                    |

|        |                                              |
|--------|----------------------------------------------|
| G6Pase | glucose-6-phosphatase                        |
| G6PC   | glucose-6-phosphatase                        |
| GC     | genome copies                                |
| GCP    | Good Clinical Practice                       |
| GGT    | gamma-glutamyl transferase                   |
| GLDH   | glutamate dehydrogenase                      |
| GLP    | Good Laboratory Practice                     |
| GSDIa  | Glycogen Storage Disease Type Ia             |
| ICH    | International Conference on Harmonization    |
| INR    | international normalized ratio               |
| ISS    | Integrated Summary of Safety                 |
| ITT    | intention-to-treat                           |
| IP     | investigational product                      |
| IRR    | infusion-related reaction                    |
| IV     | intravenous                                  |
| LDL-C  | low-density lipoprotein cholesterol          |
| LFT    | liver function test                          |
| LS     | least squares                                |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT   | modified intention-to-treat                  |
| MMRM   | mixed model for repeated measures            |
| NA     | not applicable                               |
| NCT    | National Clinical Trial                      |
| ObsRO  | observer reported outcome                    |
| PD     | pharmacodynamic                              |
| PEAP   | Primary Efficacy Analysis Period             |
| PerfO  | performance outcome                          |
| PFDD   | Patient-focused Drug Development             |
| PGIC   | Patient Global Impression of Change          |
| PK     | pharmacokinetic                              |
| PMC    | postmarketing commitment                     |
| PMR    | postmarketing requirement                    |
| PND    | Postnatal Day                                |
| PPQ    | process performance qualification            |
| PRO    | patient reported outcome                     |
| PT     | Preferred Term                               |
| qPCR   | quantitative polymerase chain reaction       |
| REMS   | risk evaluation and mitigation strategy      |
| RMAT   | Regenerative Medicine Advanced Therapy       |
| SAE    | serious adverse event                        |
| SAP    | Statistical Analysis Plan                    |
| SCR    | screening                                    |
| SEE    | Substantial evidence of effectiveness        |
| SMQ    | Standardized MedDRA Query                    |
| SOC    | System Organ Class                           |
| TBL    | total bilirubin                              |

|      |                                  |
|------|----------------------------------|
| TEAE | treatment-emergent adverse event |
| TES  | Target Enrichment Sequencing     |
| TMA  | thrombotic microangiopathy       |
| TTH  | time to hypoglycemia             |
| UACR | urine albumin creatinine ratio   |
| ULN  | upper limit of normal            |
| WT   | wild type                        |

## 1 Executive Summary

### Product Introduction

Pariglasgene breCAParvovec (DTX401; GENGLYCOS) is a nonreplicating, recombinant adeno-associated virus serotype 8 (AAV8) vector-based gene therapy designed to deliver the *G6PC* transgene to hepatocytes, enabling the production of functional glucose-6-phosphatase (G6Pase) enzyme in the liver. GENGLYCOS is administered as a single IV infusion at a dose of  $1.0 \times 10^{13}$  genome copies per kilogram (GC/kg).

### Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness of GENGLYCOS based on one adequate and well-controlled clinical investigation, Study DTX401-CL301, with confirmatory evidence. Study DTX401-CL301 demonstrated a statistically significant reduction in daily cornstarch intake in GENGLYCOS-treated patients with GSDIa compared to placebo, a surrogate endpoint reasonably likely to predict clinical benefit of improved fasting tolerance without hypoglycemia. Confirmatory evidence consists of nonclinical pharmacology evidence of dose-dependent improvements in hepatic G6Pase activity, fasting glucose, cholesterol and triglyceride levels, hepatomegaly, and nephromegaly in *G6PC* (b) (4) mice (b) (4) following IV administration of DTX401.

Study DTX401-CL301 was a randomized, double-blind, placebo-controlled Phase 3 study with a placebo-controlled period (PEAP; Weeks 1–48) followed by a crossover period (Weeks 48–96), assessing the efficacy and safety of GENGLYCOS in 46 adult and pediatric patients 8 years of age and older with GSDIa.

In Study DTX401-CL301, there was a statistically significant 31% mean difference between the treatment and placebo groups on the reduction in daily cornstarch intake from baseline to week 48, the study's primary efficacy endpoint, with directionally consistent results across secondary endpoints. These included a reduction of approximately one cornstarch dose per day, a numerical improvement in fasting tolerance as assessed by time to hypoglycemia (TTH, <54 mg/dL) during a controlled fasting challenge (CFC) (between-group difference: 0.6 hours), and relative preservation of time in the euglycemic range (70–120 mg/dL) in GENGLYCOS-treated patients (–0.51%), compared to a meaningful decline in the placebo group (–6.54%).

The favorable shifts in glycemic measures were accompanied by a small increase in time spent in the hypoglycemic range (<70 mg/dL; +3.0% vs. +0.1%; LS mean difference: +2.9%; 95% CI: 0.6%, 5.2%), with a similar directional trend observed for severe hypoglycemia (<54 mg/dL; difference: +0.51%; 95% CI: –0.15%, 1.16%), suggesting that restored G6Pase activity did not fully compensate for the reduction in cornstarch intake. Patients' global impression of change (PGI-C) reflected limited improvement, and metabolic parameters, especially plasma triglyceride levels, trended

toward worsening rather than the expected improvement after GENGLYCOS administration.

The reduction in total daily cornstarch intake may be predictive of clinical benefit, including sustained reductions in total daily cornstarch doses and improvements in fasting tolerance as assessed by TTH (70 mg/dL to 54 mg/dL) during the CFC. Cornstarch adjustments were based on objective continuous glucose monitoring measures. A Postmarketing Requirement (PMR), to be completed within 5 years post-approval, will verify this clinical benefit through a 2-year follow-up period. The study will assess total daily cornstarch doses, TTH (70 mg/dL to 54 mg/dL), nighttime cornstarch doses, metabolic biomarkers (e.g., triglycerides, uric acid, and lactate), and clinician-reported assessments of overall health.

## Benefit-Risk Assessment (BRA)

### **Benefit-Risk Summary and Assessment**

Glycogen Storage Disease Type Ia (GSDIa) is a rare, severe metabolic disease caused by a deficiency of the enzyme glucose-6-phosphatase. The incidence is approximately 1 in 100,000 to 1 in 125,000 live births worldwide. Patients with GSDIa are unable to maintain glucose homeostasis through glycogenolysis or gluconeogenesis. The disease manifests from birth with recurrent, severe hypoglycemia as the dominant acute morbidity, accompanied by a cascade of chronic metabolic complications including lactic acidosis, hyperuricemia, severe hypertriglyceridemia, hepatic steatosis, and hepatocellular adenoma formation with risk of malignant transformation. Prior to the 1980s, GSD Ia was frequently fatal in infancy. The introduction of uncooked cornstarch as standard of care (SoC) management in 1984 markedly improved survival but does not address the underlying enzymatic defect. Sustained metabolic dysregulation continues to drive progressive, cumulative end-organ damage, leaving a significant unmet need for therapy that targets the root cause of disease to restore G6Pase activity.

The safety and effectiveness of GENGLYCOS were evaluated in Study DTX401-CL301, a randomized, double-blind, placebo-controlled Phase 3 study with a placebo-controlled period (PEAP; Weeks 1–48) followed by a crossover period (Weeks 48–96), assessing safety and efficacy of GENGLYCOS in adult and pediatric patients 8 years of age and older, with GSDIa. A total of 46 patients received a single intravenous infusion of GENGLYCOS at a dose of  $1.0 \times 10^{13}$  genome copies per kilogram (GC/kg) and were included in the primary efficacy and safety analysis dataset. Prior to randomization, all patients underwent a 16-week nutritional optimization and stabilization period during which cornstarch dosing and dietary intake were adjusted based on objective continuous glucose monitoring measures. These adjustments continued throughout the study.

GENGLYCOS demonstrated a statistically significant 31% reduction in cornstarch intake on the primary endpoint, with directionally consistent results across secondary endpoints. These included a reduction of approximately one cornstarch dose per day, a numerical improvement in fasting tolerance as assessed by time to hypoglycemia (TTH, <54 mg/dL) during controlled fasting challenge (CFC) (between-group difference: 0.6 hours), and relative preservation of time in the euglycemic range (70–120 mg/dL) in GENGLYCOS-treated patients (–0.51%), compared to a meaningful decline in the placebo group (–6.54%).

These favorable shifts were accompanied by a small increase in time spent in the hypoglycemic range (<70 mg/dL; +3.0% vs. +0.1%; LS mean difference: +2.9%; 95% CI: 0.6%, 5.2%), with a similar directional trend observed for severe hypoglycemia (<54 mg/dL; difference: +0.51%; 95% CI: –0.15%, 1.16%), suggesting that restored G6Pase activity did not fully compensate for the reduction in cornstarch intake. Patients' global impression of change (PGI-C) reflected

limited improvement, and metabolic parameters, especially triglycerides, trended toward worsening rather than the expected improvement after GENGLYCOS administration.

The reduction in percent of cornstarch intake is considered a surrogate efficacy endpoint, reasonably likely to predict clinical benefit, including sustained reductions in total daily cornstarch doses and improvements in fasting tolerance as assessed by TTH (70 mg/dL to 54 mg/dL) during the CFC. Cornstarch adjustments were based on objective continuous glucose monitoring measures. A Postmarketing Requirement (PMR), to be completed within 5 years post-approval, will verify this clinical benefit through a 2-year follow-up period. The study will assess total daily cornstarch doses, TTH (70 mg/dL to 54 mg/dL), nighttime cornstarch doses, metabolic biomarkers (e.g., triglycerides, uric acid, and lactate), and clinician-reported assessments of overall health.

The safety profile was characterized based on a safety database of 58 patients in Phase 3 (n=46) and Phase 1/2 (N=12) studies. No deaths occurred in clinical studies. The primary safety signals included infusion-related reactions, hepatic toxicity, and HPA axis suppression/adrenal insufficiency. Metabolic worsening was also observed at higher rates in the DTX401 group. The observed risks were mostly mild-moderate. The serious adverse events were manageable and resolved.

We conclude that the demonstrated benefit of DTX401 outweighs the observed risks. The Applicant committed to conduct a PMR study and Postmarketing commitment (PMC) study. The PMC study will assess the theoretical risk of oncogenesis associated with AAV-based gene therapy products, and long-term safety.

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

| Dimension                    | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                  | Conclusions and Reasons                       |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>Analysis of Condition</b> | <ul style="list-style-type: none"> <li>GSD1a is an inherited metabolic disorder caused by glucose-6-phosphatase deficiency, affecting approximately 1 in 100,000–125,000 live births worldwide.</li> <li>Patients cannot maintain glucose homeostasis through glycogenolysis or gluconeogenesis, resulting in recurrent severe hypoglycemia and chronic complications including lactic acidosis,</li> </ul> | GSD1a is a rare and serious genetic condition |

| Dimension                        | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  | <p>hyperuricemia, hypertriglyceridemia, hepatic steatosis, and hepatocellular adenomas with malignant potential.</p> <ul style="list-style-type: none"> <li>Before the 1980s, GSD1a was frequently fatal in infancy; while uncooked cornstarch (introduced in 1984) improved survival, it does not address the underlying enzymatic defect, leaving a significant unmet need for a therapy that restores G6Pase activity.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Current Treatment Options</b> | <ul style="list-style-type: none"> <li>No drugs or biologics are approved for treatment of GSD1a.</li> <li>The introduction of uncooked cornstarch as SoC management in 1984 markedly improved survival but does not address the underlying enzymatic defect</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p>There is an unmet medical need for therapies that target and modify the underlying disease to improve patients' quality of life.</p>                                                                                                                                                                                                                                                                                                                                   |
| <b>Benefit</b>                   | <ul style="list-style-type: none"> <li>Study DTX401-CL301, a randomized, double-blind, placebo-controlled Phase 3 study, demonstrated efficacy in 46 patients (21 GENGLYCOS vs. 25 placebo) at Week 48 post-administration.                             <ul style="list-style-type: none"> <li>a statistically significant 31% reduction in cornstarch intake at the primary endpoint</li> <li>directionally consistent results across secondary measures, 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 (–0.4%) compared to a meaningful decline in the placebo group (–6.6%)</li> <li>GENGLYCOS-treated patients showed a slight increase in time in hypoglycemic range (glucose &lt;70 mg/dL and &lt;54 mg/dL)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>Study DTX401-CL301 is an adequate and well controlled clinical study that establishes substantial evidence of effectiveness along with confirmatory evidence from mechanistic animal data.</li> <li>A single GENGLYCOS treatment was effective in reduction of cornstarch intake</li> <li>Metabolic assessment suggested that restored G6Pase activity did not fully compensate for the reduction in cornstarch intake.</li> </ul> |

| Dimension                       | Evidence and Uncertainties                                                                                                                                                                                                                                                           | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 | <ul style="list-style-type: none"> <li>○ Triglycerides control trended toward worsening</li> <li>• Descriptive crossover data (Week 48 to Week 96) were consistent with these efficacy findings.</li> </ul>                                                                          | <ul style="list-style-type: none"> <li>• Reduction in percent of cornstarch intake serves a surrogate endpoint supporting accelerated approval.</li> <li>• A PMR study will verify clinical benefit through 2-year assessments of cornstarch dose reduction and fasting tolerance via TTH during CFC.</li> </ul>                                                       |
| <b>Risk and Risk Management</b> | <p>GENGLYCOS was associated with increased but manageable risks of:</p> <ul style="list-style-type: none"> <li>• Infusion-related reactions</li> <li>• Hepatic toxicity</li> <li>• HPA axis suppression / adrenal insufficiency</li> <li>• Worsening of metabolic control</li> </ul> | <ul style="list-style-type: none"> <li>• The size of the safety database is adequate to characterize safety profile for this rare and serious disease.</li> <li>• The overall safety assessment does not raise serious concerns that cannot be mitigated through product labeling, pharmacovigilance and a post-marketing safety observational study (PMC).</li> </ul> |

## Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

|                                     |                                                                                                                                    |                                                                            |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| <input type="checkbox"/>            | The patient experience data that was submitted as part of the application, include:                                                | Section where discussed, if applicable                                     |
| <input type="checkbox"/>            | Clinical outcome assessment (COA) data, such as                                                                                    | Section <a href="#">8.1.1</a> . Study endpoints                            |
| <input checked="" type="checkbox"/> | Patient reported outcome (PRO)                                                                                                     |                                                                            |
| <input type="checkbox"/>            | Observer reported outcome (ObsRO)                                                                                                  |                                                                            |
| <input type="checkbox"/>            | Clinician reported outcome (ClinRO)                                                                                                |                                                                            |
| <input type="checkbox"/>            | Performance outcome (PerfO)                                                                                                        |                                                                            |
| <input checked="" type="checkbox"/> | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                                                            |
| <input checked="" type="checkbox"/> | Patient-focused drug development or other stakeholder meeting summary reports                                                      | Section <a href="#">0</a> (below this table)                               |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                                                            |
| <input type="checkbox"/>            | Natural history studies                                                                                                            |                                                                            |
| <input type="checkbox"/>            | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                                                            |
| <input checked="" type="checkbox"/> | Other: (Please specify)                                                                                                            | Patient's interview data in <a href="#">8.1.4</a> – Applicant's assessment |
| <input type="checkbox"/>            | Patient experience data that was not submitted in the application, but was considered in this review.                              |                                                                            |

FDA conducted two Patient Listening sessions and an Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting with adult and pediatric GSD1a patients, pediatric caregivers, and GSD1b patient advocates to understand disease burden and treatment perspectives. Across the sessions, participants emphasized:

- Fear of life-threatening hypoglycemia
- The constant challenge of "living by the clock" with frequent cornstarch dosing
- Significant sleep deprivation affecting entire families
- Impact on quality of life, social activities, and mental health
- Strong interest in participating in clinical trials for improved treatments
- The demand for perfection in disease management with little margin for error
- The accumulation of medical comorbidities accumulating over a lifetime.

## 2 Therapeutic Context

### 2.1 Analysis of Condition

#### The Applicant's Position:

***Glycogen Storage Disease Type Ia is a rare, serious, and life-threatening disease with lack of glucose-6-Phosphatase enzyme activity and recurrent risk of life-threatening hypoglycemia***

Glycogen Storage Disease Type Ia (GSDIa) is an inborn error of carbohydrate metabolism caused by pathogenic biallelic variants of the *G6PC* gene which encodes the enzyme G6Pase (Derks et al., 2021). Patients with GSDIa have deficient or absent G6Pase enzyme activity and cannot mobilize glucose from glycogen stores or generate glucose de novo during periods of fasting. Patients primarily present clinically with impaired fasting tolerance and recurrent hypoglycemia, which can rapidly become severe and life-threatening, due to an inability to regulate endogenous glucose levels effectively. Often, patients do not experience symptomatic hypoglycemia until blood glucose levels are dangerously low and, if left untreated, hypoglycemia can lead to seizures, coma, and death (Froissart et al., 2011; Rake et al., 2002). Metabolic abnormalities (hypertriglyceridemia, hyperlactatemia, hyperuricemia, and hyperalaninemia) and other disease related complications are commonly observed; however, hypoglycemia remains a key clinical feature and important management goal in GSDIa treatment (Derks et al., 2021; Dambaska et al., 2017; Kido et al., 2013; Froissart et al., 2011; Kishnani et al., 2010; Rake et al., 2002; Weinstein et al., 2001; Rake et al., 2000). Long-term complications associated with GSDIa and abnormal glucose and metabolic control include hepatocellular adenomas, hepatocellular carcinomas, and progressive renal disease.

#### The FDA's Assessment:

The FDA concurs with the applicant's characterization of Glycogen Storage Disease Type Ia (GSDIa) as a serious and life-threatening monogenic disorder. GSDIa results from deficient glucose-6-phosphatase (G6Pase) catalytic subunit activity, which renders patients fundamentally unable to maintain glucose homeostasis through either glycogenolysis or gluconeogenesis. This enzymatic defect manifests clinically as recurrent, severe hypoglycemia, the primary acute manifestation and a historically dominant source of morbidity and mortality.

Since G6P cannot be converted to free glucose for hepatic export, it is diverted into secondary metabolic routes, including glycolysis, de novo lipogenesis, and glycogen deposition which collectively underlie the biochemical and clinical manifestations of GSDIa. Glycolytic overflow produces chronic lactic acidemia, bone demineralization, and platelet dysfunction. Pentose phosphate pathway upregulation drives excess purine synthesis, resulting in hyperuricemia, gout, and renal urate deposition. Accelerated hepatic de novo lipogenesis generates severe hypertriglyceridemia while intrahepatic lipid accumulation fuels steatosis and hepatocellular adenoma formation.

Compounding this, each hypoglycemic episode triggers a counter-regulatory hormonal surge in glucagon, cortisol, and epinephrine that accelerates glycogenolysis and gluconeogenesis in an attempt to restore blood glucose. However, because G6Pase is absent, the glucose-6-phosphate generated by these pathways has nowhere to go, further deepening its intracellular accumulation and amplifying all downstream metabolic derangements. In effect, the body's own rescue response worsens the underlying metabolic crisis. Decades of glycogen and lipid overaccumulation generate chronic hepatocellular stress, creating a permissive environment for hepatocellular adenoma formation and, in some cases, malignant transformation to hepatocellular carcinoma.

Prior to the 1980s, GSD Ia was managed with continuous nocturnal nasogastric glucose infusions, and many patients died in infancy or early childhood from intractable hypoglycemia. The introduction of uncooked cornstarch in 1984 was transformative: its slow, sustained digestion extends the inter-meal euglycemic interval, markedly improving survival and neurocognitive outcomes and enabling patients to reach adulthood for the first time.

CS intake created significant disease burden in other respects. Patients must take cornstarch around the clock to avoid life-threatening hypoglycemia, and excess cornstarch consumption also leads to metabolic complications including weight gain, insulin resistance, metabolic syndrome. As a result, improved survival due to the wide adoption of CS as the primary management approach led to a critical shift in the disease landscape. Cornstarch kept patients alive longer, but the underlying enzymatic defect persisted. G6P continued to accumulate between feeds, and rising lactate, uric acid, and triglyceride levels drove cumulative, progressive damage to the liver, kidneys, bones, and vasculature. Complications once rarely seen, such as hepatocellular adenomas, end-stage renal disease, osteoporosis, gout, and pulmonary hypertension emerged as the dominant causes of morbidity and mortality, as patients lived longer.

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 while preventing fasting hypoglycemia which can have life-threatening consequences if untreated including seizures, coma, and death. 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 CS intake/number of daily CS doses) needed to maintain a reasonable state of euglycemia without hypoglycemic events is suitable 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 of GENGLYCOS.

## 2.2 Analysis of Current Treatment Options

### The Applicant's Position:

***In GSDIa, a significant unmet need exists with current standard of care due to profound burden of treatment, fear and risk of life-threatening hypoglycemia***

There is no approved pharmacological treatment that directly addresses the underlying cause of GSDIa (i.e., the absence of glucose-6-phosphatase [G6Pase] enzyme activity). Liver transplantation is a treatment option that is potentially curative; however, it is associated with significant risks including acute rejection, perioperative bleeding, immunosuppressive treatment complications, infection, renal disease, and death (Boers et al., 2014; Labrune, 2002; Matern et al., 1999). Standard of care is aimed at symptomatic avoidance of hypoglycemia only and comprises lifelong exogenous oral glucose replacement therapy with uncooked cornstarch taken as frequently as every 3-4 hours; a highly regimented, medically prescribed diet; avoidance of fasting; and frequent monitoring of blood glucose levels (Derks et al., 2021; Kishnani et al., 2014).

Current standard of care with cornstarch is reported to be highly burdensome to patients and families, is imprecise to meet dynamic daily glycemic and metabolic needs and does not address the underlying enzymatic deficiency. Despite best adherence to cornstarch regimens patients may continue to experience recurrent hypoglycemia with life-threatening and fatal outcomes reported (Kruger, 2025) (Steunenberg, 2018). A substantial unmet need exists to address the underlying enzymatic deficiency in GSDIa, reduce dependence on exogenous glucose, reduce the risk of life-threatening hypoglycemia and improve quality of life for patients and their caregivers.

### The FDA's Assessment:

No FDA-approved therapy existed to restore G6Pase activity or address the root cause of GSD Ia. As discussed, cornstarch manages the symptoms but does not treat the disease itself. Achieving meaningful long-term benefit requires correcting the underlying enzymatic defect. Transformative gene therapy is therefore expected to restore G6Pase activity, eliminate life-threatening hypoglycemic episodes, and durably correct the metabolic dysregulation associated with GSD Ia, ultimately reducing or even eliminating the need for cornstarch altogether.

## 3 Regulatory Background

### 3.1 U.S. Regulatory Actions and Marketing History

#### The Applicant's Position:

GENGLYCOS (DTX401) is not currently registered (or approved) in the United States or any other part of the world.

#### The FDA's Assessment:

FDA concurs.

## 3.2 Summary of Presubmission/Submission Regulatory Activity

### The Applicant's Position:

Key discussions with Food and Drug Administration (FDA) were held over the course of DTX401 clinical development to align on the Phase 3 design and endpoints, including alignment on the clinical meaningfulness of the primary endpoint of reduction in cornstarch, the importance of additional related endpoints to assess glycemic control, and the totality of evidence approach to enable assessment of benefit- risk for DTX401. A summary of key regulatory designations and interactions during the DTX401 clinical development is presented in [Table](#) and [Table 2](#).

**Table 1: Applicant – Summary of Regulatory Designations with FDA**

| <b>Decision Date</b> | <b>Designation Outcome</b>                                                       |
|----------------------|----------------------------------------------------------------------------------|
| 28 Sep 2016          | Orphan Drug Designation for the treatment of GSDIa                               |
| 09 May 2018          | Fast Track designation granted for DTX401 for the treatment of GSDIa             |
| 25 Jun 2019          | RMAT designation granted for DTX401 for the treatment of GSDIa                   |
| 26 Dec 2023          | Rare Pediatric Disease Designation granted for DTX401 for the treatment of GSDIa |

GSDIa, Glycogen Storage Disease Type Ia; RMAT, Regenerative Medicine Advanced Therapy

**Table 2: Applicant – Summary of Key Regulatory Communications with FDA**

| <b>Interaction Date</b> | <b>Meeting Interaction</b>                                                                                                                                                                                                                                           |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 Oct 2020             | Combined Type B RMAT/EOP2 Meeting: discuss the design of the planned pivotal Phase 3 Study DTX401-CL301 and elements of overall development program to support a future marketing application                                                                        |
| 30 Jan 2023             | Type B CMC Meeting: discuss proposed planned PPQ strategy and commercial manufacturing plans for DTX401                                                                                                                                                              |
| 31 Jan 2023             | Type B Clinical Meeting: alignment on the clinical strategy with the proposed revisions to DTX401-CL301, the non-clinical strategy to enable development and reproductive toxicology assessment of DTX401, and the acceptability to support a marketing application. |
| 05 Dec 2024             | Type B Pre-BLA Meeting: review of available clinical data from the pivotal Phase 3 study and alignment on key elements of the planned BLA for DTX401.                                                                                                                |

BLA, biologics license application; CMC, chemistry, manufacturing, and controls; EOP2, End-of-Phase 2; RMAT, Regenerative Medicine Advanced Therapy; PPQ, process performance qualification

#### The FDA's Assessment:

FDA concurs with the timeline of the regulatory history and prior communications. Table 3 below provides a high-level summary of the clinically relevant communications referenced in the correspondence.

**Table 3: FDA – Clinical Communications**

| Meeting Date & Type                              | Clinical Comments (Primary Endpoint – Cornstarch Reduction)                                                                                                                                                                                 |
|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| October 26, 2020<br>Combined Type B<br>RMAT/EOP2 | FDA questioned whether cornstarch reduction constitutes a clinically meaningful benefit                                                                                                                                                     |
| January 31, 2023<br>Type B/EOP2                  | FDA found cornstarch reduction alone insufficient as a stand-alone primary endpoint; strongly recommended co-primary endpoints combining cornstarch reduction and TTH via CFC.                                                              |
| December 5, 2024<br>Pre-BLA Meeting              | FDA agreed cornstarch reduction may be clinically meaningful; requested additional analyses including proportion of patients who reduced/discontinued cornstarch, those who restarted, and detailed individual patient profiles/narratives. |

Source: Clinical review team

Abbreviations: EOP2, End-of-Phase 2; RMAT, Regenerative Medicine Advanced Therapy

## **4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

### **4.1 Office of Scientific Investigations (OSI)**

#### The FDA's Assessment:

Bioresearch Monitoring (BIMO) inspection assignments were issued for one foreign and two domestic clinical investigator (CI) study sites 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) and no significant BIMO inspectional observations were identified. Table 4 below summarizes site information and outcomes from the BIMO inspections.

**Table 4: FDA – Summary of Bioresearch Monitoring Inspections**

| Site ID | Firm Name                          | Location                 | FDA Form 483 Issued? | Final Classification         |
|---------|------------------------------------|--------------------------|----------------------|------------------------------|
| 102     | Areeg Hassan El-Gharbawy, MD, DSc  | Durham, North Carolina   | No                   | NAI<br>(No Action Indicated) |
| 112     | Margo Sheck Breilyn, MD, MS        | New York, New York       | No                   | NAI                          |
| 201     | John James Mitchell, FRCP, MD, MSc | Montreal, Quebec, Canada | No                   | NAI                          |

Source: FDA Bioresearch Monitoring Final Discipline Review Memo

Abbreviation: NAI, No Action Indicated

## 4.2 Product Quality

### The FDA's Assessment:

There were no major chemistry, manufacturing, and control (CMC) issues that preclude approval. For details, please see the CMC review memo.

## 4.3 Devices and Companion Diagnostic Issues

### The FDA's Assessment:

(b) (4)

(b) (4)

## 5 Nonclinical Pharmacology

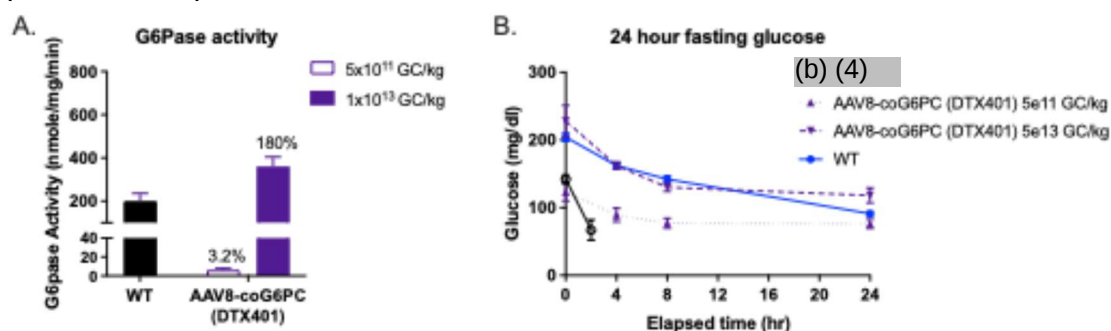
### 5.1 In Vivo Pharmacology

#### The Applicant's Position:

The pharmacology of DTX401 was investigated in two preclinical mouse models (*G6pc* (b) (4) and wild-type [WT] mice) in three studies (DTX15-401-1, WOO17-01, WOO17-07). Study DTX15-401-1 was a candidate selection and proof of concept efficacy study in the (b) (4) mouse model of GSDIa. Two dose levels were tested in male and female mice via a single intravenous dose at 10 days of age, evaluated at 14 days post dose for increased G6Pase activity and the ability to maintain blood glucose levels during a fasting challenge. In studies WOO17-01 and WOO17-07, in vivo potency of multiple DTX401 vectors, including the reference standard, was assessed in wild type mice, by measurement of G6Pase activity. Single dose intravenous (IV) administration of adeno-associated virus serotype 8 (AAV8)-codon-optimized glucose-6-phosphatase (coG6PC) to (b) (4) mice resulted in a dose-responsive increase in G6Pase activity in the liver, improvements in clinical chemistry parameters and histopathology. Normalization of blood glucose levels, cholesterol, lactic acid and triglyceride levels was

achieved with the high dose. The increase in G6Pase activity subsequently resulted in the ability of treated mice to maintain fasting glucose levels over 24 hours, avoiding hypoglycemia. Comparable and dose dependent increases in hepatic G6Pase activity in wild type C57BL/6 mice after administration of DTX401 or AAV8-coG6PC, confirmed biological activity of DTX401.

**Figure 1: Applicant – Liver Microsome G6Pase Activity (A) and Fasting Glucose Levels (B) 14 Days After Administration of AAV8-coG6PC Vectors to G6pc (b) (4) Mice; Study DTX15-401-1 (Module 4.2.1.1)**



Abbreviations: coG6PC = codon-optimized glucose-6-phosphatase; *G6pc* = glucose-6-phosphatase (mouse); G6PC = glucose-6-phosphatase (human); GC = genome copies; WT = wild-type.

Male and female (b) (4) mice were treated with AAV8-coG6PC (which was chosen as the basis for DTX401) at  $5.0 \times 10^{11}$  GC/kg or  $1.0 \times 10^{13}$  GC/kg. Mice were treated at 10 days of age and necropsied 14 days after treatment. N = 2 to 4 mice per group.

Note: Figure based on Figures 8 and 9 in Module 4.2.1.1. (b) (4) vector was removed as it was not chosen as the clinical candidate.

**Figure 1A Method summary:** G6Pase activity was measured in isolated liver microsomes using an enzymatic assay. Specifically, phosphate released from G6P due to the activity of G6Pase was measured using a  $\text{NaH}_2\text{PO}_4$  standard curve. Untreated (b) (4) mice had no G6Pase activity.

**Figure 1B Method summary:** Fourteen days after AAV8-coG6PC administration, mice were fasted for twenty-four hours, and blood glucose levels were measured at 0, 4, 8, and 24 hours from beginning of fast. Untreated (b) (4) mice were only fasted for two hours, due to their inability to maintain fasting blood glucose levels.

#### The FDA's Assessment:

In vivo pharmacology studies conducted in 2-week-old glucose-6-phosphatase, catalytic subunit 1 (G6PC) (b) (4) mice (b) (4) demonstrated that IV administration of DTX401 at dose levels of  $5.0 \times 10^{11}$  or  $1.0 \times 10^{13}$  gc/kg led to dose-dependent increases in hepatic G6Pase activity and fasting glucose levels. At the higher dose level of  $1.0 \times 10^{13}$  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  $9.0 \times 10^{11}$  gc/kg of GENGLYCOS™. These data provide confirmatory mechanistic evidence in support of

the effectiveness of DTX401. Please refer to the Pharmacology/Toxicology review memo (Studies #2-7) for a detailed review of this data.

## 5.2 ADME/PK

### The Applicant's Position:

The absorption, distribution, metabolism, excretion (ADME) properties of DTX401 were investigated in 3 preclinical models across 7 studies ([Table](#)). Following a single intravenous administration of DTX401, widespread biodistribution of vector genome DNA was detected across tissues in mice, with the liver exhibiting the highest level (**VPT4185**). Dose-dependent increases in hepatic vector genome DNA were observed following IV administration of DTX401 in mice (**DTX401-23-0004**) and monkey (**DTX401-22-0006**) up to  $7 \times 10^{13}$  GC/kg. Hepatic human G6PC mRNA and G6Pase protein expression correlated with vector genome DNA levels, and liver transduction persisted for up to 3 months in mice (**VPT4185**) and 6 months in monkeys (**DTX401-22-0006**). Vector shedding in mice occurred in feces, urine, and semen, and vector genome DNA levels became undetectable by Days 29 (feces/urine) and 92 (semen) (**DTX401-22-0009**). Despite measurable vector genome DNA in the blood, liver, placenta and reproductive organs in pregnant mice or F0 mice, no detectable levels were found in fetuses or F1 offsprings in the Embryo-fetal Developmental (EFD) and germline transmission studies (**DTX401-23-0004**, **DTX401-23-0006**).

**Table 5: Applicant – ADME Summary**

| Overview                                                                             |                                                               |                                                 |                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Type of Study                                                                        | Model                                                         | Study # / eCTD                                  | Main findings                                                                                                                                                                                                                     |
| <b>Absorption</b>                                                                    | NA (DTX401 is given through IV directly into the circulation) |                                                 |                                                                                                                                                                                                                                   |
| <b>Distribution</b>                                                                  |                                                               |                                                 |                                                                                                                                                                                                                                   |
| DTX401: Proof of Concept and Candidate Selection                                     | Mice (b) (4)                                                  | <a href="#">DTX15-401-1 / Module 4.2.2.3</a>    | Dose-dependent increase in DTX401 vector genome DNA and human G6Pase protein expression (as measured by its enzyme activity) in the liver was observed from $5 \times 10^{11}$ to $1 \times 10^{13}$ GC/kg                        |
| DTX401: Single Dose Intravenous Toxicity and Biodistribution Study in C57BL/6N Mouse | Mice (C57BL/6N)                                               | <a href="#">VPT4185 / Module 4.2.2.3</a>        | Transgene expression in the liver increased in a time-dependent manner from Day 4 and reached a plateau by Day 29 to 92. Widespread biodistribution of vector genome DNA detected across tissues. No sex difference was observed. |
| A Single Dose Juvenile Toxicity Study of DTX401 in C57BL/6N Mice                     | Mice (C57BL/6N)                                               | <a href="#">DTX401-21-0007 / Module 4.2.2.3</a> | As the age of mice increased from PND 2 to 28 at the time of DTX401 administration, greater amounts of vector genome DNA were found in the liver on Day 29 and Day 92 post dose.                                                  |

| <b>Overview</b>                                                                                          |                     |                                                 |                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------|---------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Type of Study</b>                                                                                     | <b>Model</b>        | <b>Study # / eCTD</b>                           | <b>Main findings</b>                                                                                                                                                                             |
| An Embryo-fetal Development Study of DTX401 by Intravenous Injection in Mice                             | Mice (C57BL/6N)     | <a href="#">DTX401-23-0004 / Module 4.2.2.3</a> | Levels of vector genome DNA in the placenta were approximately 37- to 193-fold lower than that found in the liver. No fetal liver had detectible levels of vector genome DNA.                    |
| A Germline Transmission Study in Offspring of Mice Following a Single Intravenous Dose of DTX401 in Mice | Mice (C57BL/6N)     | <a href="#">DTX401-23-0006 / Module 4.2.2.3</a> | Despite the presence of vector genome DNA in the blood, liver and reproductive organs of F0 mice, blood and liver samples from F1 offsprings were all BLOQ for vector genome DNA on PND 15 – 21. |
| A 6 Month Single Dose Intravenous Pharmacology and Toxicology Study of DTX401 in Cynomolgus Monkeys      | Monkey (Cynomolgus) | <a href="#">DTX401-22-0006 / Module 4.2.2.3</a> | A dose-dependent increase in hepatic vector genome DNA was observed from $1 \times 10^{13}$ to $7 \times 10^{13}$ GC/kg of DTX401 independent of the animal's baseline ADA status.               |
| <b>Metabolism</b>                                                                                        | N/A                 |                                                 |                                                                                                                                                                                                  |
| <b>Excretion</b>                                                                                         |                     |                                                 |                                                                                                                                                                                                  |
| A 3-Month Single Dose Toxicity Study of DTX401 by Intravenous Injection in Mice                          | Mice (C57BL/6N)     | <a href="#">DTX401-22-0009 / Module 4.2.2.5</a> | Levels of vector genome DNA in excreta were the highest on Day 2 and declined over time with levels reaching BLOQ/BLOD in feces/urine and semen by Day 29 and Day 92, respectively.              |

ADA, anti-drug-antibody; BLOD, below limit of detection; BLOQ, below limit of quantification; G6Pase, glucose-6-phosphatase; GC, genome copies; IV, intravenous; NA, not applicable; PND, Postnatal Day

#### The FDA's Assessment:

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  $7 \times 10^{13}$  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  $7 \times 10^{13}$  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. Please refer to the Pharmacology/Toxicology review memo (Studies #5, #8-13) for a detailed review of this data.

## **6 Clinical Pharmacology**

### **6.1 Executive Summary**

#### The FDA's Assessment:

The clinical pharmacology evaluation of GENGLYCOS (pariglasgene breCAPARVovec, DTX401) includes pharmacokinetics (biodistribution and vector shedding), pharmacodynamics (reduction in daily cornstarch intake), and immunogenicity assessment. After administration of DTX401, 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 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. DTX401 treatment resulted in statistically significant reduction in cornstarch intake compared to Placebo at Week 48 post-dosing. Please refer to Section [8](#) for detailed review. Both humoral and cellular immune responses against DTX401 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 proposed dosing regimen: a single dose of GENGLYCOS at  $1.0 \times 10^{13}$  genomes copies/kg body weight administered via intravenous (IV) infusion is acceptable. The clinical pharmacology results support accelerated approval for GENGLYCOS (pariglasgene breCAPARVovec, DTX401) 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).

### **6.2 Summary of Clinical Pharmacology Assessment**

#### **6.2.1 Pharmacology and Clinical Pharmacokinetics**

##### Data:

The mechanism of action of DTX401 (Section [6.3.1](#)) is supported by nonclinical data and clinical efficacy data. Biodistribution of DTX401 vector genome DNA in blood and vector shedding in urine, stool, and saliva were assessed in 12 patients at multiple time points in Studies 401GSDIA01 and 401GSDIA02.

##### The Applicant's Position:

The vector genome DNA was cleared from saliva within 7 weeks and from urine and stool within 13 weeks post-infusion in patients. The risks associated with vector shedding are negligible. The blood pharmacokinetics (PK) and vector shedding data collected in Study 401GSDIA01 can be used to support drug labeling.

The FDA's Assessment:

FDA concurs with the Applicant's position.

## **6.2.2 General Dosing and Therapeutic Individualization**

### **6.2.2.1 General Dosing**

Data:

The recommended dose of DTX401 is  $1.0 \times 10^{13}$  genome copies per kilogram (GC/kg) body weight, administered as a single intravenous infusion. Two weeks after DTX401 administration, prophylactic corticosteroids should be administered for a minimum of 8 weeks.

The Applicant's Position:

The totality of clinical efficacy and safety data, and nonclinical PK/pharmacodynamics (PD), as well as previously accumulated knowledge of AAV8 vectors, supports the selection of DTX401  $1.0 \times 10^{13}$  GC/kg per Droplet Digital polymerase chain reaction (ddPCR) with prophylactic steroids as the registrational dose regimen for the general population.

The FDA's Assessment:

FDA concurs with the Applicant's position.

### **6.2.2.2 Therapeutic Individualization**

Data:

Covariate analyses of Phase 3 efficacy data based on intrinsic and extrinsic factors did not detect any clinically meaningful covariate effects on the efficacy endpoint. In the Primary Efficacy Analysis Period (PEAP), in both pediatric (8 – 17 years of age) and adult subgroups, significantly greater reductions in cornstarch were observed in the DTX401 group vs the Placebo group. In DTX401-treated subjects in the PEAP, pediatric subjects had lower reductions in cornstarch compared with adult subjects (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.16.1, 14.2.1.1.16.2).

The Applicant's Position:

No dose adjustment is needed for any subpopulation.

The FDA's Assessment:

FDA concurs with the Applicant's position.

## **6.3 Comprehensive Clinical Pharmacology Review**

### **6.3.1 General Pharmacology and Pharmacokinetic Characteristics**

#### **6.3.1.1 Pharmacokinetic Characteristics**

Data:

DTX401 is an AAV8 based gene therapy designed to deliver a copy of the *glucose-6-phosphatase (G6PC)* gene to hepatocytes, resulting in the production of normally functioning G6Pase. DTX401 retains native human *G6PC* promoter and enhancer elements and is therefore expected to be under the control of normal hormonal regulatory responses (eg, suppression of G6Pase from insulin, stimulation of G6Pase from cortisol). Based on nonclinical data, following treatment with DTX401, transgene expression and subsequent G6Pase activity is expected within one week, but it may take several weeks to achieve maximum levels.

Biodistribution of vector genome DNA in blood and vector shedding in urine, stool, and saliva was assessed in 12 patients at multiple time points in Studies 401GSDIA01 and 401GSDIA02 (401GSDIA01 and 401GSDIA02 CSR Sections 11.1 and 11.2). 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. At a dose of  $6.0 \times 10^{12}$  GC/kg measured using quantitative polymerase chain reaction (qPCR) (which is equivalent to the recommended dose of  $1.0 \times 10^{13}$  GC/kg measured using ddPCR, the highest individual peak concentration observed in blood was  $6.8 \times 10^7$  GC/100 ng blood DNA and in the stool was  $1.7 \times 10^6$  GC/100 ng stool DNA. Blood vector genome DNA in most patients reached below the limit of detection (BLOD) approximately 24 weeks post infusion. Clearance of vector DNA was defined as measurement of 3 consecutive results below the limit of detection. Based on this definition, vector genome DNA was cleared from saliva within 7 weeks and from urine and stool within 13 weeks post-infusion.

#### The Applicant's Position:

Because DTX401 is deficient in replication, vector genome is rapidly cleared from blood circulation, and the levels of vector genome in saliva, urine, and stool are low, individuals in contact with patients receiving DTX401 (eg, healthcare providers, family members) are unlikely to be exposed to levels of DTX401 that could potentially be hazardous. Additionally, the shedding of infectious vector particles is inherently limited, and the pathogenic potential of shed vector components is extremely low (Whomsley et al., 2021). Therefore, the risks associated with vector shedding are negligible. As transmission to untreated individuals is a low probability event based on the vector shedding data from Study 401GSDIA01, monitoring of individuals for vector shedding did not occur in the Phase 3 study, DTX401-CL301. Blood PK was also not analyzed in Study DTX401-CL301 as the extent of product dissemination from the site of administration and the kinetics of product clearance was well characterized in Studies 401GSDIA01 and 401GSDIA02.

The blood PK and vector shedding data collected in Study 401GSDIA01 are used to support drug labeling. The clinical drug substance for the Phase 1 study 401GSDIA01 was manufactured at the clinical manufacturing site using the (b) (4) process. The clinical drug substance for the Phase 3 study 401GSDIA03 was also manufactured at the clinical manufacturing site using the (b) (4) process. There was no (b) (4) process. Comparability was established between the (b) (4) processes prior to introducing the (b) (4) material into clinical trials. The commercial drug substance will be manufactured at the commercial manufacturing facility (Ultragenyx facility in

Bedford, MA) using the (b) (4) process. The manufacturing changes are not expected to affect PK and vector shedding of DTX401. Analytical comparability studies (see reports in Modules 3.2.S.2.6 and 3.2.P.2.3) designed per International Conference on Harmonization (ICH) Q5E “Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process” demonstrated the comparability between the drug products used in the Phase 1/2 and Phase 3 studies and the comparability between the Phase 3 product and commercial product.

#### The FDA’s Assessment:

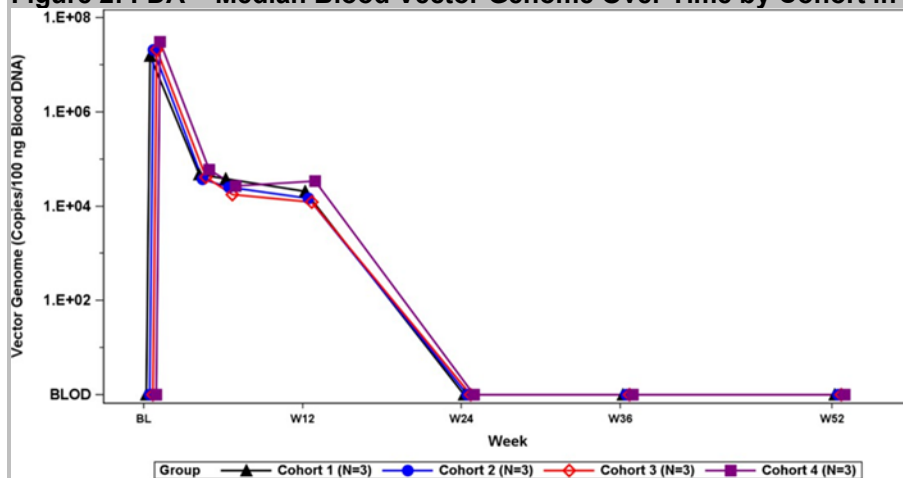
FDA concurs with the Applicant’s position.

Biodistribution of vector genome DNA in blood and vector shedding of DTX401 were evaluated in Study 401GSDIA01.

#### **Biodistribution of DTX 401 Vector Genome DNA in Blood**

As shown in [Figure 2](#), peak concentrations of circulating vectors in blood were observed at the first post-dose assessment on Day 2 for all subjects in Study 401GSDIA01. Cohort 1 had lower median blood vector genome levels at Day 2 as compared to Cohorts 2, 3, and 4. After reaching peak levels, circulating vectors decreased over time with 4 distinct phases: a rapid decrease phase between Week 0 and Week 4, a slow decrease phase between Week 4 and Week 12, a second rapid decrease phase between Week 12 and Week 24 and the last phase when levels declined below the limit of detection (BLOD). The first concentration BLOD was around Week 24 post-dose. This profile represents a rapid distribution of vectors from blood to the respective tissues, followed by a redistribution of vectors over time. Steroid treatment did not appear to affect vector levels or the pattern of vector decrease over time in blood, suggesting that DTX401 tissue distribution and redistribution were not affected by steroid treatment.

**Figure 2: FDA – Median Blood Vector Genome Over Time by Cohort in Log Scale**



Source: Applicant. EDR. Module 2, section 2.7.2. Summary of Clinical Pharmacology Studies. Figure 2

| Table 6. FDA – Vector Genome Determination in Blood and Vector Shedding for Individual Subjects |                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
|-------------------------------------------------------------------------------------------------|---------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Parameter                                                                                       |                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| Patient No.                                                                                     | 1                   | 2                  | 3                  | 4                  | 5                  | 6                  | 7                  | 8                  | 9                  | 10                 | 11                 | 12                 |
| Blood<br>(copies/100<br>ng blood<br>DNA)                                                        |                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| Peak GC                                                                                         | 3.5×10 <sup>6</sup> | 15×10 <sup>6</sup> | 15×10 <sup>6</sup> | 50×10 <sup>6</sup> | 20×10 <sup>6</sup> | 15×10 <sup>6</sup> | 65×10 <sup>6</sup> | 16×10 <sup>6</sup> | 21×10 <sup>6</sup> | 68×10 <sup>6</sup> | 22×10 <sup>6</sup> | 30×10 <sup>6</sup> |
| Time to<br>Peak                                                                                 | Day 2               | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              | Day 2              |
| First value<br>BLOD                                                                             | Week<br>24          | Week<br>36         | Week<br>24         | Week<br>24         | Week<br>24         | Week<br>24         | Week<br>42         | Week<br>35         | Week<br>27         | Week<br>36         | Week<br>24         | Week<br>24         |
| Confirmed<br>negative                                                                           | Week<br>52          | NC                 | Week<br>52         | NC                 | Week<br>52         | Week<br>53         | Week<br>76         | Week<br>51         | Week<br>36         | NC                 | Week<br>52         | NC                 |
| Saliva<br>(copies/100<br>ng saliva<br>DNA)                                                      |                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| Peak GC                                                                                         | 3061                | 1945               | 782                | 10954              | 5012               | 6577               | 15865              | 26230              | 3619               | 15368              | 18269              | 3211               |
| Time to<br>Peak                                                                                 | Day 8               | Day 8              | Day 8              | Day 8              | Day 8              | Day 8              | Day 4              | Day 3              | Day 5              | Day 4              | Day 4              | Day 4              |
| First value<br>BLOD                                                                             | Week 4              | Week 4             | Day 22             | Week 5             | Week 4             | Week 4             | Week 4             | Week 4             | Week 4             | Day 21             | Day 22             | Day 21             |
| Confirmed<br>negative                                                                           | Week 6              | Week 6             | Week 5             | Week 7             | Week 6             | Week 6             | Week 6             | Week 6             | Week 6             | Week 6             | Week 6             | Week 6             |
| Urine<br>(copies/100<br>ng urine<br>DNA)                                                        |                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |
| Peak GC                                                                                         | BLOD                | 494                | BLOD               | 243                | BLOD               | 1376               | 25888              | 3529               | 45                 | 13711              | 25232              | 163                |
| Time to<br>Peak                                                                                 | N/A                 | Day 8              | N/A                | Day 8              | Day 8              | Day 8              | Day 4              | Day 3              | Day 5              | Day 4              | Day 4              | Day 4              |
| First value<br>BLOD                                                                             | N/A                 | Day 22             | N/A                | Day 22             | Day 8              | Week 5             | Week 6             | Day 13             | Day 13             | Week 6             | Week 4             | Day 11             |
| Confirmed<br>negative                                                                           | Day 13              | Week 6             | Day 13             | Week 5             | Day 22             | Week<br>10         | Week 11            | Week 6             | Week 4             | Week<br>11         | Week 6             | Week 6             |
| Stool<br>(copies/100                                                                            |                     |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |                    |

|                    |                    |                    |                    |                     |                    |                    |                      |                     |                     |                    |                    |                    |
|--------------------|--------------------|--------------------|--------------------|---------------------|--------------------|--------------------|----------------------|---------------------|---------------------|--------------------|--------------------|--------------------|
| ng stool DNA)      |                    |                    |                    |                     |                    |                    |                      |                     |                     |                    |                    |                    |
| Peak GC            | 28×10 <sup>3</sup> | 12×10 <sup>3</sup> | 64×10 <sup>3</sup> | 105×10 <sup>3</sup> | 99×10 <sup>3</sup> | 24×10 <sup>3</sup> | 1663×10 <sup>3</sup> | 1.7×10 <sup>3</sup> | 502×10 <sup>3</sup> | 98×10 <sup>3</sup> | 17×10 <sup>3</sup> | 28×10 <sup>3</sup> |
| Time to Peak       | Day 8              | Day 8              | Day 8              | Day 8               | Day 8              | Day 8              | Day 13               | Day 13              | Day 4               | Day 8              | Day 13             | Day 4              |
| First value BLOD   | Week 5             | Day 22             | Day 22             | Week 4              | Week 5             | Week 5             | Week 11              | Week 6              | Week 4              | Week 6             | Week 5             | Week 5             |
| Confirmed negative | Week 8             | Week 7             | Week 5             | Week 6              | Week 9             | Week 7             | Week 13              | Week 12             | Week 6              | Week 8             | Week 9             | Week 7             |

Source: Applicant. EDR. Study 401GSDIA01 Clinical Study Report, Table 21

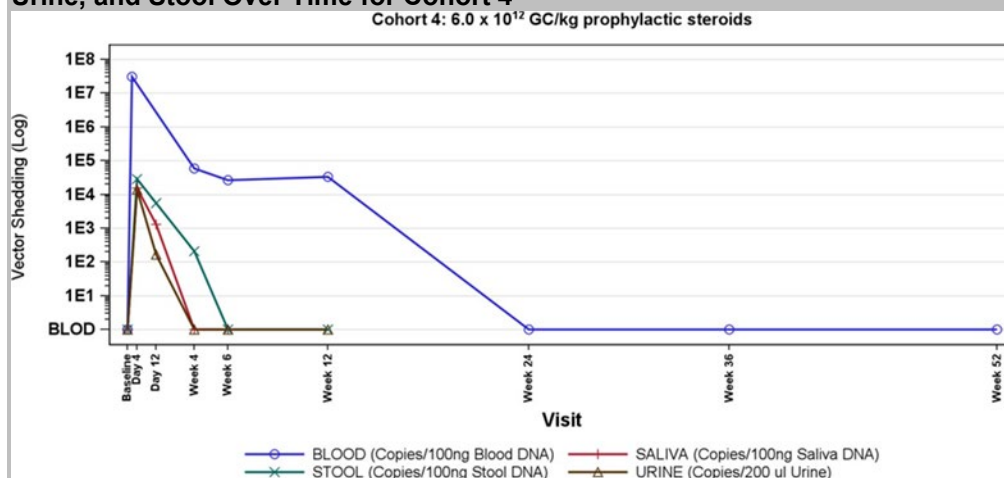
Note: Confirmed negative time point is the time at which the third consecutive negative result was reported. Values reported as “Baseline” in the CSR have been updated to “N/A” in this table to be more accurate as the value was undetectable.

Abbreviations: BLOD, below level of detection; GC, genome copies; NC, not confirmed

## Vector Shedding in Saliva, Urine and Stool

Results of vector shedding from saliva, urine, and stool are summarized in Figure 3. Excretion of viral vectors in saliva increased until 1 week post-dose and then gradually decreased over time, reaching BLOD by 4 weeks post-dose for most subjects in Study 401GSDIA01. The duration of measurable vectors in saliva appears to be dose-independent, and treatment with steroids did not affect the vector shedding in saliva. The excretion of viral vectors in the other excreta followed similar patterns as saliva. The median levels of viral vectors appeared to be the greatest in stool, followed by saliva and urine for all treatment cohorts. The peak concentration of viral vectors in stool was generally lower than that in blood by 2 to 3 orders of magnitude. All subjects were confirmed negative (based on 3 consecutive BLOD values) for the excretion of vectors in saliva by Week 7, and in stool and urine by Week 13.

**Figure 3: FDA – Median Vector Genome Determination in Blood and Vector Shedding in Saliva, Urine, and Stool Over Time for Cohort 4**



Source: Applicant. EDR. Module 2, section 2.7.2. Summary of Clinical Pharmacology Studies. Figure 3

### 6.3.1.2 Immunogenicity

#### The FDA's Assessment:

Immunogenicity assessments against DTX401 include humoral (anti-AAV8 antibody and anti-G6Pase antibody) and cellular immune responses against AAV8 and G6Pase.

#### **Anti-AAV8 Antibody Response**

In Studies 401GSDIA01 and 401GSDIA02, all 12 subjects were seronegative at Baseline for both binding and neutralizing anti-AAV8 antibodies. All 12 subjects seroconverted by Week 4 (first post-dose measurement) and remained positive at all subsequent visits through Week 260 (5 years), indicating a durable, persistent antibody response. No apparent impact on efficacy or safety was observed.

### **Anti-G6Pase Antibody Response**

In Studies 401GSDIA01 and 401GSDIA02, all subjects were anti-G6Pase negative at baseline. Only 1 of 12 subjects developed a transient positive anti-G6Pase titer (1:20) at week 156, subsequent samples at Week 208 and 260 were negative. At Week 260, all 6 subjects with available data were negative. The clinical significance of anti-G6Pase antibodies is not clear.

### **T Cell Response to AAV8**

T cell response against AAV8 was evaluated using enzyme-linked immunosorbent spot assay (ELISpot assay). Ten of twelve subjects had a positive baseline cellular response to AAV8; all 12 showed increased responses post-dose. In Cohorts 1–3, cellular AAV8 responses in 6 of 9 subjects preceded ALT elevations and decreased with reactive prednisone use. Responses were heterogeneous beyond Week 52.

### **T Cell Response to G6Pase**

T cell response against G6Pase was evaluated using ELISpot assay. Two of twelve subjects were positive at baseline; 10 of 12 showed increased G6Pase cellular responses post-dosing. Temporal correlation with ALT was observed in only 2 subjects. Responses beyond Week 52 were heterogeneous with no clear ALT association.

Please refer to Section [8.2.4.11](#) for immunogenicity assessment results of Study DXT401-CL301.

### **Impact of Immunogenicity Against DTX401 on Efficacy**

The impact of immune responses against DTX401 on efficacy was assessed using results of Study DTX401-CL301.

### **Impact of Anti-AAV8 Antibodies on Efficacy**

In Study DTX401-CL301, a total of 4 subjects with pre-existing or transiently positive anti-AAV8 antibodies at or around the time of dosing were nonetheless treated with DTX401. Two subjects had pre-existing anti-AAV8 antibodies on the day of receiving DTX401 treatment. Both of the two subjects showed reduction in cornstarch intake and change were within the range of subjects without pre-existing anti-AAV8 antibodies. The percentage of glucose values in the hypoglycemic ranges (< 70 mg/dL and < 54 mg/dL) in these two subjects were also within the range of subjects without pre-existing anti-AAV8 antibodies. There was no apparent impact of anti-AAV8 antibodies on efficacy.

### **Impact of Anti-G6Pase Antibodies on Efficacy**

All subjects were negative for anti-G6Pase antibodies at Baseline. In the DTX401 group, treatment-emergent anti-G6Pase titers were observed in 7 out of 21 subjects. Of those, 6 subjects had a persistent response (defined in Section [4](#)) and 1 subject had a transient response. At Week 48, 4 subjects in the DTX401 group had a positive response. In the Crossover Placebo – DTX401 group, treatment-emergent anti-G6Pase titers were observed in 4 out of 19 subjects on follow-up. Of those, 1 subject had a

persistent response and 3 subjects were positive only at the last available visit. The highest observed titer of anti-G6Pase was 1:40. Among subjects with treatment-emergent anti-G6Pase antibodies, there's no apparent impact on efficacy (as evaluated by percent change in cornstarch reduction, percent change in glucose values in the < 70 mg/dL and < 54 mg/dL range).

### **Impact of Cellular Immune Responses against G6Pase on Efficacy**

In Study DTX401-CL301, cellular immune response against G6Pase was assessed. There were 3 subjects in the DTX401 group and 2 subjects in the Crossover Placebo→DTX401 group with positive G6Pase ELISpot prior to DTX401 administration. There was no apparent difference in the percentage of cornstarch reduction at Week 48 in subjects with a positive cellular response to G6Pase (ELISpot) at Baseline as compared with those subjects who were negative for the cellular response to G6Pase (ELISpot) at Baseline. During the PEAP, there were no DTX401 responders; 18 of 21 evaluable patients were all ELISpot non-responders (DTX401-CL301 Week 96). During the follow-up period, there were 10 of 21 (47.6%) DTX401-dosed subjects that were ELISpot responders (eg between week 48 and week 96) and 12 of 19 (63.2%) Crossover Placebo→DTX401 group responders (DTX401-CL301 Week 96). The higher incidence of ELISpot responders between weeks 48 and 96 may have been due to steroid use, which may impact the ELISpot assay. The clinical significance of G6Pase cellular immune response on efficacy is unknown based on heterogeneous responses from Individual subject. The use of steroids maybe one of the co-founding factors for this observation.

## **6.3.2 Clinical Pharmacology Questions**

### **6.3.2.1 Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?**

#### Data:

Percent change from Baseline in daily cornstarch intake was a pharmacodynamic endpoint and a key efficacy endpoint in Studies 401GSDIA01, 401GSDIA02, and DTX401-CL301. Refer to Section [8.1](#) for more information.

In the dose-finding studies (Studies 401GSDIA01 and 401GSDIA02), DTX401 was evaluated at two dose levels:  $2.0 \times 10^{12}$  GC/kg (Cohort 1) and  $6.0 \times 10^{12}$  GC/kg (Cohorts 2-4) determined by qPCR. To provide supportive evidence of effectiveness, the Applicant conducted exploratory dose-response and vector genome exposure-response analyses for multiple efficacy endpoints (daily cornstarch intake, time to first hypoglycemic event during controlled fasting challenge, and percent of normoglycemic glucose levels). Dose-response or vector genome exposure-response relationships for efficacy were not observed using data from Cohort 1 ( $2 \times 10^{12}$  GC/kg) and Cohorts 2-4 ( $6 \times 10^{12}$  GC/kg) (refer to Section [6.3.2.2](#)).

In the Phase 3 study, DTX401 was tested at one dose level only ( $1.0 \times 10^{13}$  GC/kg per ddPCR, which is equivalent to the  $6.0 \times 10^{12}$  GC/kg dose per qPCR), and PK samples were not collected because blood PK was well characterized in Studies 401GSDIA01

and 401GSDIA02. Thus, no dose-response or exposure-response analyses were conducted for subjects enrolled in the Phase 3 study, DTX401-CL301.

The Applicant's Position:

Although dose-response or vector genome exposure-response relationships for efficacy were not observed, the consistent reduction in daily cornstarch intake in the three studies supports the effectiveness of DTX401.

The FDA's Assessment:

Please refer to Section 8 for detailed FDA's assessment.

**6.3.2.2 Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication Is Being Sought?**

Data:

The proposed dose ( $1.0 \times 10^{13}$  GC/kg per ddPCR, which is equivalent to the  $6.0 \times 10^{12}$  GC/kg dose [qPCR]) with prophylactic steroids was selected based on the totality of the data from clinical efficacy, and safety, and nonclinical PK/PD of DTX401, as well as previously accumulated knowledge of AAV8 vectors.

In the first-in-human study (401GSDIA01), DTX401 was evaluated at 2 dose levels:  $2.0 \times 10^{12}$  GC/kg (Cohort 1, N = 3) and  $6.0 \times 10^{12}$  GC/kg (Cohorts 2-4, N = 3 per cohort) determined by qPCR with long-term follow-up of subjects occurring in the extension study (401GSDIA02). The reduction in daily cornstarch intake was maintained for more than 5 years among the 4 cohorts. Mean cornstarch reductions in Cohorts 2-4 were 64% at Week 52 and 70% at the last available visit, consistent with cornstarch reductions across all Phase 1/2 subjects (68% at Week 52, 74% at last available visit) (401GSDIA02 CSR Table 14.2.1.4, Figure 16.2.6.1.5.2).

A DTX401 dose higher than  $6.0 \times 10^{12}$  GC/kg was not tested in Study 401GSDIA01 because when the dose of DTX401 was increased by 3-fold in Cohorts 2-4 compared with Cohort 1, no further decrease in daily cornstarch intake was observed, suggesting that further increases in dose could add risks without adding significant benefit. Exploratory dose-response and vector genome exposure-response analyses were conducted for multiple efficacy endpoints (daily cornstarch intake, time to first hypoglycemic event during controlled fasting challenge, and percent of normoglycemic glucose levels). Dose-response or vector genome exposure-response relationships for efficacy were not observed using data from Cohort 1 ( $2 \times 10^{12}$  GC/kg) and Cohorts 2-4 ( $6 \times 10^{12}$  GC/kg). Based on satisfactory tolerability and clinical benefit in Study 401GSDIA01, the  $6.0 \times 10^{12}$  GC/kg dose with prophylactic steroids was determined to be the optimal biological dose to be used in the Phase 3 study (DTX401-CL301).

Between the 401GSDIA01 study and the DTX401-CL301 study, the assay to determine the DTX401 vector genome titer (GC/mL) was updated from qPCR to a more precise, *G6PC*-specific ddPCR method. A conversion factor was established based upon a comparison of samples analyzed using the qPCR- or ddPCR-based concentration

method, resulting in the selection of a dose of  $1.0 \times 10^{13}$  GC/kg (by ddPCR) for the Phase 3 study DTX401-CL301, which is equivalent to the  $6.0 \times 10^{12}$  GC/kg dose (by qPCR).

The proposed dose of  $1.0 \times 10^{13}$  GC/kg (by ddPCR) is also supported by the dose-response relationships of DTX401 and other AAV8 vectors observed in nonclinical species. AAV8 vectors showed dose-dependent hepatocyte transduction efficiency and transgene expression in C57BL/6 mice following IV doses of  $5.0 \times 10^{10}$  to  $7.2 \times 10^{12}$  GC/mouse (equivalent to  $1.25 \times 10^{12}$  to  $1.8 \times 10^{14}$  GC/kg in human based on liver mass ratio) without saturation in transduction, and 100% of the mouse hepatocytes were transduced at the dose of  $7.2 \times 10^{12}$  GC/mouse without toxicity (Nakai et al., 2005).

In nonclinical species, single IV doses of DTX401 ranging from  $1.0 \times 10^{11}$  to  $1.0 \times 10^{13}$  GC/kg increased G6Pase activity in the liver of wild-type C57BL/6 mice in a dose-dependent manner. In the G6Pase- $\alpha$  (b) (4) mouse model, a  $5.0 \times 10^{11}$  GC/kg dose of DTX401 and a  $1.0 \times 10^{13}$  GC/kg dose of DTX401 increased the mean G6Pase activity to 3.2% (N = 4) and 180% (N = 3) of wild-type level, respectively. Fasting glucose assessments in these G6Pase- $\alpha$  (b) (4) mice showed that correction of G6Pase activity to 3.2% of wild-type level in the  $5.0 \times 10^{11}$  GC/kg group protected against hypoglycemia but did not restore initial glucose homeostasis. In contrast, the  $1.0 \times 10^{13}$  GC/kg group maintained normoglycemia and had blood glucose profiles comparable to wild-type mice at all time points measured. In cynomolgus monkeys, an IV dose of  $1.0 \times 10^{13}$  or  $7.0 \times 10^{13}$  GC/kg of DTX401 resulted in a 4.5-fold higher vector genome of DTX401 and 13.3-fold higher human G6PC mRNA in liver tissue at the higher dose. Together, these data demonstrate a dose-response relationship of DTX401 in mice and monkeys, showing that a higher dose of DTX401 would be expected to increase expression of G6Pase and improve correction of metabolic abnormalities in patients with GSDIa.

Differences in steroid treatment regimens affected hepatic function and may have affected cornstarch reduction in Cohorts 1-4 in the Studies 401GSDIA01 and 401GSDIA02. Subjects in Cohorts 1 and 2 received reactive steroids (with the exception of 1 subject in Cohort 1), subjects in Cohort 3 received optimized reactive steroids, and subjects in Cohort 4 received prophylactic steroids on study Day 1 (pre-DTX401) to minimize vector induced hepatic effects and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations. Elevations in aminotransferases (ALT and/or AST) above the upper limit of normal were observed in all subjects during the first 6 months following DTX401 administration. These events were considered to be due to an immune-mediated etiology consisting of ALT and AST elevations, and were nonserious, transient, and resolved with corticosteroid treatment where administered (reactively or proactively). Subjects in Cohort 4 had faster and greater reductions in cornstarch over 12 weeks post-DTX401 administration compared to subjects in the other 3 cohorts. However, subjects had challenges completely tapering off the steroids. A prophylactic steroid regimen beginning on Day 15 was selected as the treatment for Phase 3 study DTX401-CL301, to coincide with the estimated timing of immune activation.

In all three clinical studies (401GSDIA01, 401GSDIA02 and DTX401-CL301), DTX401 demonstrated an acceptable safety profile at the proposed dose ( $1.0 \times 10^{13}$  GC/kg per ddPCR with prophylactic Day 15 steroids).

The Applicant's Position:

The totality of clinical efficacy and safety data, and nonclinical PK/PD, as well as previously accumulated knowledge of AAV8 vectors, supports the selection of DTX401  $1.0 \times 10^{13}$  GC/kg per ddPCR (which is equivalent to the  $6.0 \times 10^{12}$  GC/kg dose by qPCR) with prophylactic steroids as the registrational dose regimen.

The FDA's Assessment:

FDA concurs with the Applicant's position.

**6.3.2.3 Is An Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors (e.g., Race, Ethnicity, Age, Performance Status, Genetic Subpopulations, etc.)?**

Data:

All subjects received the registrational dose ( $1.0 \times 10^{13}$  GC/kg\_per ddPCR) and no alternative dosing was evaluated in the Phase 3 trial. Reduction in cornstarch intake during the PEAP was assessed in the following subgroups: pediatric vs adult, subjects taking an average of  $\geq 4$  daily cornstarch doses vs  $< 4$  daily cornstarch doses, Tanner stage, Glycosade use at Baseline, blood glucose level at Baseline, region, and subjects with or without detectable anti-AAV8 antibodies and is summarized in DTX401-CL301 Week 96 CSR Section 10.1.1.2. In the PEAP, in both pediatric (8 – 17 years of age) and adult subgroups, significantly greater reductions in cornstarch were observed in the DTX401 group vs the Placebo group. In DTX401-treated subjects in the PEAP, pediatric subjects had lower reductions in cornstarch compared with adult subjects. During the double-blinded PEAP, Investigators may have exerted greater caution in cornstarch reduction in pediatric subjects compared to adults. The reduction in cornstarch intake from Baseline to Week 48 during PEAP in other subgroups was generally consistent with the primary analysis.

Subgroup analyses by intrinsic and extrinsic factors (pediatric vs adult, body weight, body mass index [BMI], AST/ALT, drug substance manufacturing process, and baseline G6Pase enzyme-linked immunosorbent spot assay [ELISpot] status) for the percent change from Baseline to 48 weeks post-DTX401 treatment in daily cornstarch intake were conducted for the DTX401 and Crossover Placebo →DTX401 groups. In the Crossover Placebo →DTX401 group, pediatric subjects had slightly lower reductions in cornstarch than adult subjects; cornstarch reductions in both subgroups were greater in the Crossover Period compared to the PEAP (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.16.1, 14.2.1.1.16.2, 14.2.1.1.16.3, 14.2.1.1.16.4). In the DTX401 group, greater reductions in cornstarch were observed in subjects with higher than median body weight and BMI than those with lower body weight/BMI, but the 95% CIs of the subgroups overlapped. This potential association was not observed in the Crossover group (DTX401-CL301 CSR Tables 14.2.1.1.1.2.2.1, 14.2.1.1.1.2.2.2, 14.2.1.1.1.2.3.1,

14.2.1.1.1.2.3.2, 14.2.1.1.1.2.4.1, 14.2.1.1.1.2.4.2, 14.2.1.1.1.2.5.1, 14.2.1.1.1.2.5.2). Four subjects who screened negative for anti-AAV8 antibodies had low titers at either Baseline or Week 48 (their dosing day) or were Crossover Placebo→DTX401 group subjects that seroconverted and sero-reverted prior to DTX401 dosing. The percent change from Baseline to Week 48 in daily cornstarch intake in these four individuals was within the range of results for the population. No obvious differences in the reduction in total daily cornstarch intake were observed in the subgroup analyses by other intrinsic and extrinsic factors (Module 2.7.2 Section 2.3.2.2).

The Applicant's Position:

Overall, covariate analyses of Phase 3 efficacy data based on intrinsic and extrinsic factors did not detect any clinically meaningful covariate effects on the efficacy endpoint. Thus, no dose adjustment is needed for any subpopulation.

The FDA's Assessment:

FDA concurs with the Applicant's position.

**6.3.2.4 Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What Is The Appropriate Management Strategy?**

Data/Applicant's Position:

Not applicable for intravenously administered DTX401.

The FDA's Assessment:

FDA concurs with the Applicant's position.

## 7 Sources of Clinical Data

### 7.1 Table of Clinical Studies

Data:

The clinical program of DTX401 included a dose-finding Phase 1/2 study, 401GSDIA01, its long-term extension, 401GSDIA02, and a pivotal Phase 3 study, DTX401-CL301, that collectively assessed DTX401 efficacy and safety in GSDIa (Table 7).

**Table 7: Applicant – Completed and Ongoing Clinical Trials Relevant to this BLA**

| <b>Trial Identity/<br/>NCT no.</b>                     | <b>Trial Design/<br/>Status</b>                                                                                                                                                    | <b>Regimen/<br/>schedule/<br/>route</b>                          | <b>Study Endpoints</b>                                                                                                                                                                                                                                                                                                   | <b>Treatment<br/>Duration/<br/>Follow Up</b>                                                                                                    | <b>No. of<br/>patients<br/>enrolled</b>                                                                                                                                            | <b>Study<br/>Population</b>                                                                                                                          | <b>No. of<br/>Centers<br/>and<br/>Countries</b> |
|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>Controlled Study to Support Efficacy and Safety</b> |                                                                                                                                                                                    |                                                                  |                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                 |                                                                                                                                                                                    |                                                                                                                                                      |                                                 |
| DTX401-<br>CL301<br><br>NCT05139316                    | Phase 3,<br>randomized,<br>double-blind,<br>placebo-<br>controlled<br>efficacy and<br>safety study<br><br>Ongoing;<br>Clinical cutoff<br>date for BLA<br>dossier: 03<br>March 2025 | Single IV<br>dose of<br>$1.0 \times 10^{13}$<br>GC/kg<br>(ddPCR) | Primary: %CFB at<br>W48 in daily<br>cornstarch intake<br>for DTX401 vs<br>placebo groups<br><br>Secondary<br>subject to<br>multiplicity: CFB<br>to W48 in # of<br>total daily doses<br>of cornstarch,<br>CFB to W48 in %<br>of glucose values<br>in hypoglycemic<br>range (70 mg/dL),<br>PGIC assessment<br>score at W48 | Total follow-up<br>post-DTX401:<br>144 weeks<br>• PEAP: 48<br>weeks<br>• Crossover<br>Period: 48<br>weeks<br>• Follow-up<br>Period: 48<br>weeks | 49<br>randomized<br><br>46 subjects<br>(20<br>pediatric)<br>dosed with<br>blinded IP at<br>Day 1<br><br>36 subjects<br>(11<br>pediatric)<br>dosed with<br>blinded IP at<br>Week 48 | ≥ 8 years of<br>age with<br>confirmed<br>diagnosis of<br>GSDIa, with<br>optimized<br>and stable<br>nutrition,<br>glycemic,<br>and clinical<br>status | 17<br>centers in<br>8<br>countries              |

| Other Studies Pertinent to the Review of Efficacy and Safety |                                                                                                   |                                                                                                |                                                                                                                                                        |                                                                  |                                                |                                                     |                          |
|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------|--------------------------|
| 401GSDIA01<br><br>NCT03517085                                | Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study<br><br>Complete     | Single IV dose of $2.0 \times 10^{12}$ GC/kg or $6.0 \times 10^{12}$ GC/kg (qPCR) <sup>a</sup> | <u>Primary:</u> Safety<br><br><u>Secondary:</u> CFB in time to first hypoglycemic event during CFC at 12, 24, and 52 weeks after DTX401 administration | Total follow-up post-DTX401: 52 weeks                            | 12 subjects enrolled and dosed with DTX401     | ≥ 18 years of age with confirmed diagnosis of GSDIa | 6 centers in 4 countries |
| 401GSDIA02<br><br>NCT03970278                                | Phase 1/2, long-term follow-up study to evaluate safety and efficacy<br><br>Complete <sup>b</sup> | NA                                                                                             | <u>Primary:</u> Safety<br><br><u>Secondary:</u> CFB in time to first hypoglycemic event during a CFC                                                   | Up to 6 years after administration of DTX401 in Study 401GSDIA01 | 12 enrolled – no IP administered in this study | Received DTX401 in Study 401GSDIA01                 | 6 centers in 4 countries |

<sup>a</sup> Equivalent to  $1.0 \times 10^{13}$  GC/kg by Droplet Digital PCR (ddPCR) administered in Phase 3.

<sup>b</sup> 27 June 2024 was the clinical cutoff date for data included in the dossier; study was completed in February 2025. Per FDA request, the final CSR for Study 401GSDIA02 was included in the final BLA rolling submission (Seq 0002).

AE, adverse event; BLA, Biologics License Application; CFB, change from Baseline; CFC, controlled fasting challenge; ddPCR, Droplet Digital polymerase chain reaction; DLTs, dose-limiting toxicities; GC, genome copies; GSDIa, Glycogen Storage Disease Type Ia; IV, intravenous; IP, investigational product; NA, not applicable; NCT, National Clinical Trial; PEAP, primary efficacy analysis period; PGIC, Patient Global Impression of Change; TEAE, treatment-emergent adverse event

#### The Applicant's Position:

Across studies, 3 independent treatment periods evaluated DTX401 efficacy and safety in subjects with GSDIa, including 2 separate, double-blind, controlled treatment periods in the Phase 3 study and an open-label Phase 1/2 study. These studies included a broad and representative patient population aged 8 years and older with GSDIa.

Selection of clinical endpoints in these trials involved careful consideration of multiple aspects of GSDIa that are most important and clinically meaningful to patients and aligned with Patient-focused Drug Development (PFDD) guidelines (FDA, 2020-2023).

#### The FDA's Assessment:

The clinical program of DTX401 consists of the following studies:

- Phase 1/2 study (Study 401GSDIA01): Completed
- A Phase 3 study (Study DTX401-CL301): Ongoing. As of the March 3, 2025 data cutoff, all patients had completed the Week 96 assessment and were in the post-Week 96 Follow-up Period (Weeks 96–144).

Long Term Follow Up (LTFU) studies:

- Study 401GSDIA02: LTFU study for patients who completed Phase 1/2 study
- Disease Monitoring Program (DMP): LTFU study for patients who completed Phase 3 study

The safety and efficacy evaluations of DTX401 were primarily focused on data from Phase 3 study (Study DTX401-CL301).

The efficacy and safety findings from the Phase 1/2 study are not integrated with those of the Phase 3 study due to differences in study design as detailed in Section [8.1.2](#).

The long term follow up studies (401GSDIA02 and DMP) were designed to monitor the long-term safety and durability of efficacy of DTX401 following Phase 1/2 and Phase 3 studies. Data from these long-term follow-up studies were not used to support this BLA.

## **8 Statistical and Clinical Evaluation**

### **8.1 Review of Relevant Individual Trials Used to Support Efficacy**

#### **8.1.1 Study DTX401-CL301**

##### **8.1.1.1 Trial Design**

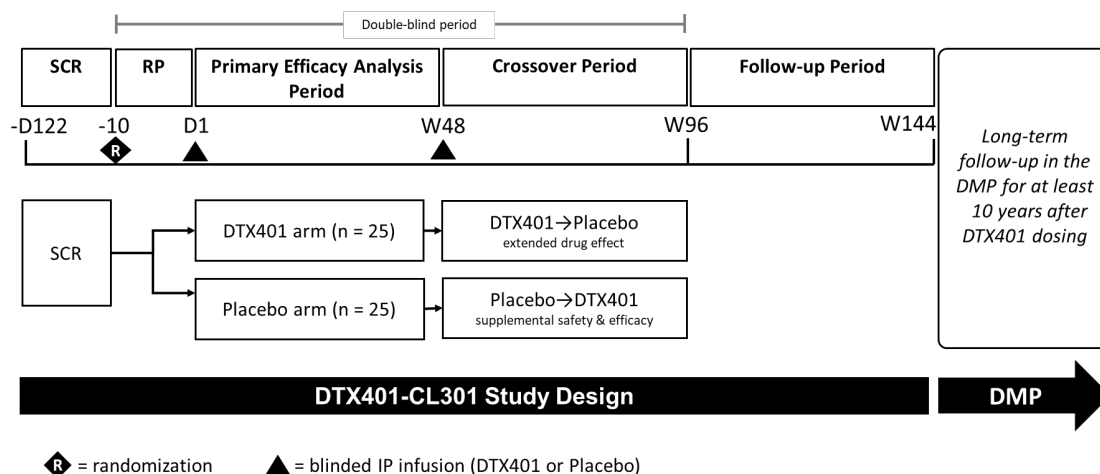
#### The Applicant's Description:

Study DTX401-CL301 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study to determine the efficacy and confirm the safety of DTX401 in subjects 8 years and older with GSDIa.

Eligible subjects were randomly assigned in a 1:1 ratio to receive blinded DTX401 ( $1.0 \times 10^{13}$  GC/kg by ddPCR) or placebo. Additionally, subjects received a prophylactic blinded immunomodulatory regimen of prednisolone or placebo to minimize hepatic reactions that may occur following administration of AAV8 gene therapy.

Upon completion of a double-blind 48-week PEAP, subjects crossed over in a blinded manner (ie, subjects who received DTX401 at Day 1 received placebo at Week 48 and subjects who received placebo at Day 1 received DTX401 at Week 48) and were followed through a double-blind 48-week Crossover Period up to Week 96. All subjects will be followed until Week 144 in the study, allowing evaluation of durability of DTX401 efficacy and safety.

**Figure 4: Applicant – Study DTX401-CL301 Schema**



DMP, Disease Monitoring Program; SCR, screening; RP, randomization period

## Nutrition Optimization and Stabilization

In alignment with draft guidance from the FDA on drug development in inborn errors of metabolism, to address potential bias, variability and improve interpretability of results following DTX401 treatment (FDA, 2023), subjects underwent a period of nutrition optimization and stabilization up to 16 weeks during the Screening Period to adjust cornstarch and diet on a weekly basis to minimize the occurrence of hypoglycemia and maximize time in euglycemia prior to randomization and dosing with blinded investigational product (IP). To meet eligibility for randomization and dosing, all subjects were required to demonstrate stability on an optimized nutritional regimen for at least 4 weeks.

### The FDA's Assessment:

Clinical Trial Registry Identifiers: ClinicalTrials.gov: NCT04491604

### Objective

Safety and Efficacy of DTX401 in pediatric (8 to < 18 years) and adult ( $\geq 18$  years) patients with GSDIa.

The study was conducted at 17 centers across the United States, Italy, Brazil, Canada, Denmark, Germany, the Netherlands, and Spain.

DTX401 was the name of the investigational product used in clinical studies.

### Design Overview

A Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study.

Patients were enrolled and randomly in a 1:1 ratio to receive either DTX401 or placebo.

The study consisted of the following sequential periods (Applicant's Figure 4):

- Screening Period (up to 16 weeks, Day –122 to Day –10): This period included nutrition optimization and a minimum 4-week stabilization phase to confirm glycemic, cornstarch, and dietary stability prior to randomization (refer to eligibility criteria). As shown in Schedule of Assessments (SoE) Table 9 and Table 10, eligibility criteria and assessments were performed throughout this period.
- Randomization Period (Day –10 to Day 0)
- Baseline assessment (Day 0): Eligibility criteria and baseline assessments were repeated.
- Primary efficacy assessment period (PEAP, Weeks 1–48): Randomized patients receive DTX401 or placebo on Day 1.
  - DTX401 (Pariglasgene Brecaaparvovec): A single dose of  $1.0 \times 10^{13}$  GC/kg was administered via peripheral intravenous (IV) infusion according to the infusion protocol (Table 8).
  - Dosing cap: Patients weighing more than 90 kg received a dose capped at the 90 kg weight-based calculation.
  - Placebo: A single peripheral IV infusion of normal saline (0.9% sodium chloride), supplied in a matching infusion bag.

**Table 8: FDA – DTX401 Infusion Rate Per Protocol\***

| Timing      | Weight < 40 kg<br>(100 mL bag) | Weight ≥ 40 kg (<br>250 mL bag) |
|-------------|--------------------------------|---------------------------------|
| 0–60 min    | 3 mL/hr                        | 6 mL/hr                         |
| 61–80 min   | 8 mL/hr                        | 18 mL/hr                        |
| 81–100 min  | 15 mL/hr                       | 38 mL/hr                        |
| 101–120 min | 30 mL/hr                       | 75 mL/hr                        |
| 121–180 min | 80 mL/hr                       | 200 mL/hr                       |

Source: Clinical review team

\*Following anaphylaxis in 2 patients within 1–6 minutes of administration, Protocol Amendment 3 (06 July 2023) and Pharmacy Manual v6.0 (12 July 2023) revised the infusion rate to a slow, staged approach (up to 7 hours) and added infusion reaction management guidelines.

- Cross Over (Weeks 48 to 96)
  - Patients originally assigned to DTX401 received placebo, while eligible patients originally assigned to placebo received a single blinded IV infusion of

DTX401 at  $1.0 \times 10^{13}$  GC/kg (if still eligible per Study Continuation Criteria, including absence of anti-AAV8 antibodies).

- Follow up: Weeks 96 to 144 (ongoing)

### **Corticosteroid Use**

Oral corticosteroids (prednisone or equivalent) or matching placebo should be initiated 2 weeks after DTX401 administration at 60 mg/day (or 1.0 mg/kg/day for patients weighing less than 60 kg), maintained for 4 weeks, then tapered stepwise (40 → 30 → 20 → 10 → 5 mg/day) over approximately 4 weeks. Additional immunomodulatory therapy may be considered as clinically indicated.

The Applicant justified initiating corticosteroids two weeks after DTX401 administration based on Phase 1/2 experience and the disease characteristics of GSD Ia. Capsid-directed immune responses and associated liver enzyme elevations typically emerge between Weeks 4 and 12 post-infusion; therefore, beginning corticosteroids at the time of infusion would not prevent immune memory formation and would only result in prolonged, unnecessary exposure. This is especially important for patients with GSD Ia, whose underlying metabolic condition makes it a clinical priority to limit their exposure to corticosteroids.

### **Premedication**

Subjects should receive the following premedications, or matching placebo, 30 to 60 minutes prior to investigational product administration as prophylactic treatment for potential infusion-related reactions.

- Acetaminophen/paracetamol: 12.5 mg/kg, up to a maximum of 1 g, oral
- 2nd generation H1 antagonist (e.g., cetirizine, loratadine, fexofenadine): 10 mg (cetirizine), oral
- H2 antagonist (e.g., famotidine): 0.5 mg/kg, up to a maximum of 40 mg, oral

## Assessments

The monitoring and assessment schedule is shown in Table 9 (Year 1) and Table 10 (Year 2) below.

**Table 9: FDA – Schedule of Events, Year 1**

| Period                                                     | Screen           | Rand  | BL       | Primary Efficacy Analysis Period      |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          | Holdin<br>g<br>Visit(s)<br>a | E<br>W   |
|------------------------------------------------------------|------------------|-------|----------|---------------------------------------|-------------------------------------------------|------------------------------|-------------|-------------|-------------|--------------------------|-------------|------------------|----------------------|----------------------|----------------------|--------------------------|------------------------------|----------|
| Visit Time<br>(Day/Week)                                   | D-122 to<br>D-10 | D-10  | D0       | D1<br>-<br>D2<br>Pr<br>e-<br>do<br>se | D1-<br>D2<br>Dos<br>e/<br>Pos<br>t-<br>dos<br>e | D15<br>Start<br>Stero<br>ids | W4          | W5          | W6          | Week<br>ly<br>W7-<br>W11 | D84/<br>W12 | D168<br>/<br>W24 | D21<br>0/<br>W3<br>0 | D2<br>52/<br>W3<br>6 | D2<br>94/<br>W4<br>2 | D3<br>36<br>/<br>W<br>48 | Holdin<br>g<br>Visit(s)<br>a | E<br>W   |
| Visit Window<br>(Days)                                     | -                | -     | -        | Pr<br>e-<br>do<br>se                  | Dos<br>e/<br>Pos<br>t-<br>dos<br>e              | -                            | +3          | +3          | +3          | +3                       | +3          | +14              | +14                  | +14                  | +14                  | +7                       | +14                          | -        |
| Visit Type                                                 | oPt              | Phone | In<br>Pt | In<br>Pt                              | InPt<br>b                                       | Phon<br>e                    | oPt/H<br>Hc | oPt/H<br>Hc | oPt/H<br>Hc | oPt/H<br>Hc              | oPt/H<br>Hc | oPt/H<br>Hc      | Pho<br>ne            | InPt                 | Ph<br>one            | In<br>Pt                 | oPt/HH<br>c                  | In<br>Pt |
| ASSESSMENTS                                                |                  |       |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |
| Informed<br>consent                                        | X                |       |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |
| Review<br>eligibility<br>criteria                          | X                | X     |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |
| Demographics                                               | X                |       |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |
| Relevant<br>medical history                                | X                |       |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |
| GSDIa medical<br>history                                   | X                |       |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |
| Height <sup>d</sup>                                        | X                |       | X        |                                       |                                                 |                              |             |             |             |                          |             | X                |                      |                      |                      | X                        |                              | X        |
| Weight                                                     | X                |       | X        |                                       | X                                               |                              | X           |             | X           |                          | X           | X                | X                    | X                    | X                    | X                        |                              | X        |
| Relevant prior<br>medications/t<br>herapies/proc<br>edures | X                |       |          |                                       |                                                 |                              |             |             |             |                          |             |                  |                      |                      |                      |                          |                              |          |

| Period                                                                                                                                                          | Screen | Rand | BL | Primary Efficacy Analysis Period |   |   |   |   |   |   |   |   |   |   |   |   | Holdin<br>g<br>Visit(s)<br>a | E<br>W |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|------|----|----------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|------------------------------|--------|
| Relevant concomitant medications/therapies/procedures                                                                                                           | X      | X    | X  | X                                | X | X | X | X | X | X | X | X | X | X | X | X | X                            | X      |
| Dispense/administer oral prednisolone/placebo kite                                                                                                              |        |      |    |                                  | X |   |   |   |   |   |   |   |   | X |   |   |                              |        |
| Collect oral prednisolone/placebo kit                                                                                                                           |        |      |    |                                  |   |   |   |   |   |   |   |   |   |   |   | X |                              |        |
| Prednisolone/placebo monitoring phone calls (Refer to Table 14)                                                                                                 |        |      |    |                                  |   | X |   |   |   |   |   |   |   |   |   |   |                              |        |
| Early morning cortisol and ACTH <sup>f</sup> (to be obtained 24 hours after completing the prednisolone/placebo taper; any abnormal levels reviewed by the CIC) |        |      |    |                                  |   |   |   |   |   |   |   |   |   |   |   |   |                              |        |
| GSD FAD eDiary <sup>g</sup>                                                                                                                                     |        |      | X  |                                  |   |   |   |   |   |   |   | X |   |   |   | X |                              | X      |
| GSD FAD (weekly version) <sup>g</sup>                                                                                                                           |        |      |    |                                  |   |   |   |   |   |   |   | X |   |   |   | X |                              |        |
| PGIS <sup>g</sup>                                                                                                                                               | X      |      | X  |                                  |   |   | X | X | X | X |   | X |   |   |   | X |                              |        |

| Period                                                              | Screen | Rand | BL | Primary Efficacy Analysis Period |   |   |   |   |   |   |   |   |   |   |   |   | Holdin<br>g<br>Visit(s)<br>a | E<br>W |
|---------------------------------------------------------------------|--------|------|----|----------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|------------------------------|--------|
| PGIC <sup>g</sup>                                                   | X      |      | X  |                                  |   |   |   |   |   |   |   | X | X | X |   | X |                              | X      |
| PGIC-CTT <sup>g</sup>                                               |        |      |    |                                  |   |   |   |   |   |   |   | X |   |   |   | X |                              |        |
| EQ-5D-5L/EQ-5D-Y <sup>h</sup>                                       | X      |      | X  |                                  |   |   |   |   |   |   |   |   | X |   | X |   |                              |        |
| HEOR assessments                                                    | X      |      |    |                                  |   |   |   |   |   |   |   |   |   | X |   | X |                              | X      |
| AEs/SAEs                                                            | X      | X    | X  | X                                | X | X | X | X | X | X | X | X | X | X | X | X | X                            | X      |
| Vital sign measurements <sup>i</sup>                                |        |      | X  | X                                | X |   | X | X | X | X | X | X | X | X | X | X | X                            | X      |
| Complete physical examination <sup>j</sup>                          | X      |      | X  |                                  | X |   |   |   |   |   |   |   |   |   |   |   |                              |        |
| Targeted physical examination <sup>j</sup>                          |        |      |    |                                  |   |   | X |   |   |   |   | X | X | X | X | X |                              |        |
| 12-lead ECG                                                         | X      |      | X  |                                  | X |   |   |   |   |   |   |   |   |   |   |   |                              |        |
| G6PC genotyping <sup>k</sup>                                        | X      |      |    |                                  |   |   |   |   |   |   |   |   |   |   |   |   |                              |        |
| HBV, HCV, HIV                                                       | X      |      |    |                                  |   |   |   |   |   |   |   |   |   |   |   |   |                              |        |
| Serum pregnancy test (women of childbearing potential only)         | X      |      |    |                                  |   |   |   |   |   |   |   |   |   |   |   |   |                              |        |
| Urine pregnancy test (women of childbearing potential) <sup>j</sup> |        |      | X  |                                  |   |   |   |   | X |   | X | X | X | X | X | X |                              | X      |
| Standard clinical chemistry panel - Central Lab <sup>m</sup>        | X      |      | X  | X                                | X |   | X | X | X | X | X | X | X | X | X | X | X                            | X      |
| Lactate <sup>n</sup>                                                |        |      | X  |                                  |   |   | X |   |   |   | X |   |   |   |   |   |                              |        |
| Standard clinical chemistry                                         |        |      | X  | X                                |   |   |   |   |   |   |   | X |   | X |   |   |                              |        |

| Period                                                                                                                               | Screen | Rand | BL | Primary Efficacy Analysis Period |   |  |   |   |   |  |   |   |   |   |   |   | Holdin<br>g<br>Visit(s)<br>a | E<br>W |
|--------------------------------------------------------------------------------------------------------------------------------------|--------|------|----|----------------------------------|---|--|---|---|---|--|---|---|---|---|---|---|------------------------------|--------|
| panel - Local Lab <sup>m</sup>                                                                                                       |        |      |    |                                  |   |  |   |   |   |  |   |   |   |   |   |   |                              |        |
| STAT glucose and lactate during CFC <sup>o</sup>                                                                                     |        |      | X  |                                  |   |  |   |   |   |  | X |   |   |   |   | X |                              |        |
| Cortisol and other HPA axis tests as needed <sup>p</sup>                                                                             |        |      |    |                                  |   |  |   |   |   |  |   |   | X |   |   | X |                              |        |
| Cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine, and ketones during CFC <sup>o</sup> |        |      | X  |                                  |   |  |   |   |   |  | X |   |   |   |   | X |                              |        |
| Hematology, coagulation panel, urinalysis - Local Lab                                                                                |        |      | X  |                                  | X |  |   |   |   |  |   |   |   |   |   |   |                              |        |
| Hematology, coagulation panel, urinalysis - Central Lab                                                                              |        |      | X  |                                  | X |  | X |   | X |  | X | X | X | X | X | X |                              |        |
| 9-panel urine drug screens                                                                                                           | X      |      |    |                                  |   |  |   | X |   |  |   |   |   |   |   |   |                              |        |
| 24-hour urine collection <sup>q</sup>                                                                                                |        |      | X  |                                  |   |  |   |   |   |  |   |   |   |   |   | X |                              |        |
| AAV8 TAb assay <sup>r</sup>                                                                                                          | X      |      |    |                                  |   |  |   |   |   |  | X |   |   |   |   |   |                              |        |
| AAV8 binding antibody IgG                                                                                                            | X      |      |    |                                  | X |  | X |   | X |  | X | X |   |   | X | X |                              |        |

| Period                                                                             | Screen | Rand | BL | Primary Efficacy Analysis Period |   |  |   |   |   |  |   |   |   |   |   |   | Holdin<br>g<br>Visit(s)<br>a | E<br>W |
|------------------------------------------------------------------------------------|--------|------|----|----------------------------------|---|--|---|---|---|--|---|---|---|---|---|---|------------------------------|--------|
| testing<br>(b) (4)                                                                 |        |      |    |                                  |   |  |   |   |   |  |   |   |   |   |   |   |                              |        |
| Cell-mediated<br>immune<br>response to<br>G6Pase<br>(ELISpot)                      | X      |      |    |                                  |   |  |   | X |   |  | X |   |   |   |   | X |                              |        |
| Complement<br>activity (C3,<br>C4, SC5b-9,<br>CH50, AH50,<br>MBL)                  |        |      | X  | X                                | X |  |   |   |   |  |   |   |   |   |   |   |                              |        |
| Serum<br>tryptase                                                                  |        |      | X  | X                                | X |  |   |   |   |  |   |   |   |   |   |   |                              |        |
| Anti-G6Pase<br>antibody<br>assay                                                   | X      |      |    |                                  |   |  |   |   |   |  | X |   |   |   |   | X |                              | X      |
| Optional<br>future<br>research<br>samples                                          |        |      | X  |                                  | X |  |   |   |   |  | X |   |   |   |   | X |                              | X      |
| Liver<br>ultrasound <sup>t</sup>                                                   | X      |      |    |                                  |   |  |   |   |   |  |   |   |   | X |   |   |                              |        |
| SMBG <sup>u</sup>                                                                  |        |      | X  |                                  | X |  | X |   | X |  |   | X | X | X | X | X | X                            |        |
| CGM <sup>v</sup>                                                                   | X      |      | X  |                                  | X |  | X |   | X |  |   | X | X | X | X | X | X                            |        |
| Assessment of<br>prescribed<br>cornstarch and<br>cornstarch<br>intake <sup>w</sup> | X      |      | X  |                                  | X |  | X |   | X |  |   | X | X | X | X | X | X                            |        |
| Assessment of<br>prescribed diet<br>and dietary<br>intake <sup>w</sup>             | X      |      | X  |                                  | X |  | X |   | X |  |   | X | X | X | X | X | X                            |        |
| Controlled<br>fasting<br>challenge <sup>x</sup>                                    |        |      | X  |                                  |   |  |   |   |   |  |   | X |   |   |   | X |                              | X      |

| Period                                       | Screen | Rand | BL | Primary Efficacy Analysis Period |   |  |  |  |  |  |  |   |   |  |  | Holdin<br>g<br>Visit(s)<br>a | E<br>W |
|----------------------------------------------|--------|------|----|----------------------------------|---|--|--|--|--|--|--|---|---|--|--|------------------------------|--------|
| CFC<br>Questionnaire <sup>x</sup>            |        |      | X  |                                  |   |  |  |  |  |  |  | X |   |  |  | X                            | X      |
| Subject<br>entry/exit<br>interview           |        | X    |    |                                  |   |  |  |  |  |  |  |   |   |  |  | X                            | X      |
| Subject<br>number<br>assigned in<br>IRT      | X      |      |    |                                  |   |  |  |  |  |  |  |   |   |  |  |                              |        |
| Randomization<br>in IRT                      |        | X    |    |                                  |   |  |  |  |  |  |  |   |   |  |  |                              |        |
| IP<br>administration<br>scheduling in<br>IRT |        | X    |    |                                  |   |  |  |  |  |  |  |   | X |  |  |                              |        |
| Premedication <sup>y</sup>                   |        |      |    | X                                |   |  |  |  |  |  |  |   |   |  |  |                              |        |
| IP infusion                                  |        |      |    |                                  | X |  |  |  |  |  |  |   |   |  |  |                              |        |

Source: Table 3 in Clinical protocol of Study DTX401-CL301 submitted in Module 5 of the BLA submission, Pages 21-25.

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

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

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

d In subjects ≥18 years of age, height will be assessed only at Screening, Baseline, Week 48, and Early Withdrawal visits.

e Subjects randomly assigned to DTX401 in Year 1 will receive an oral prophylactic prednisolone regimen; subjects randomly assigned to placebo IP infusion will receive a matching oral placebo regimen. Oral prophylactic prednisolone or matching placebo will be initiated 14 days after IP administration (Day 15).

f To be obtained 24 hours after completing the prednisolone/placebo taper; any abnormal levels should be reviewed by the Central Independent Committee (CIC).

g The GSD FAD eDiary will be completed electronically by the subject every morning and evening for 14 days before the Baseline Visit and for 7 days before each applicable postbaseline study visit. The GSD FAD (weekly version) will be completed on paper at the clinic site visit. The PGIC and PGIS will be completed electronically via the eDiary on the day before the applicable study visit. The PGIC-CTT will be completed on paper at the applicable postbaseline study visits.

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

i Vital signs include seated systolic and diastolic blood pressure (mm Hg), heart rate (beats/min), respiration rate (breaths/min), and temperature (degrees C). Performed at every visit before additional assessments, except on days of IP infusion when performed more frequently per section 9.1.4.

j Complete physical examination includes head, eyes, ears, nose, and throat; skin; abdomen with documentation of liver and spleen size; and endocrine, metabolic, peripheral and central nervous systems, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems. Targeted physical examination includes skin; abdomen; respiratory, cardiovascular, and gastrointestinal systems. Tanner pubertal stage assessed at Baseline and all postdosing inpatient visits for pediatric subjects <18 years of age.

k G6PC mutation analysis will not be waived unless results have been obtained previously from the same laboratory conducting the analysis and are in the subject's medical records.

l A serum pregnancy test must also be conducted in the event of a positive urine pregnancy test result.

m Standard clinical chemistry assessments listed in Table 19. Samples collected after vital signs and other noninterventive assessments and at least 2-4 hours after the subject's last meal. If liver function tests between Weeks 4 and 11 are stable, the assessment schedule may be reduced from weekly to every two weeks at the Investigator's discretion.

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

o Samples specific to the CFC will be collected at the beginning and end of the CFC or more frequently at the Investigator's discretion. During the CFC, subjects should be wearing their CGM and capillary glucose should be assessed and recorded at each CFC time point. For pediatric subjects weighing <45 kg, samples other than glucose and lactate are optional and per Investigator's discretion.

p Morning cortisol and other exploratory tests of the HPA axis should be performed as necessary prior to the CFC, approximately 1 week before the Week 36 and Week 48 Visit.

q Urine will be collected for 24 hours prior to the CFC at Baseline and Week 48 and sent to the Central Laboratory for analysis.

r It is recommended that the Screening sample be collected at the time written informed consent is provided. The AAV8 TAb assay should be repeated prior to the second IP administration if more than 6 months have elapsed since the last measurement.

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

t At Investigator's discretion, an alternative imaging modality (e.g., CT or MRI) can be used in place of liver ultrasound if more clinically appropriate.

u SMBG must be performed at least 4 times a day in the 1-week period prior to each postbaseline scheduled visit at Weeks 24, 30, 36, 42, and 48. Additional SMBG assessments may be performed per standard of care or at the Investigator's discretion or if the subject is symptomatic.

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

w Subjects must record their cornstarch and diet intake daily for at least 4 weeks before the Baseline Visit. Subjects will record cornstarch intake daily for at least 1 week before Weeks 24, 30, 36, and 42 visits, and at least 4 weeks before Week 48. Subjects must record daily diet for 3 consecutive days prior to Weeks 24, 30, 36, 42, and 48 visits.

x The CFC requires a 24-hour inpatient hospitalization or admission in a research facility and includes a dinner meal personalized for each subject, followed by a prefasting cornstarch dose and up to 15 hours of fasting.

y Premedication to be administered 30 to 60 minutes prior to the start of blinded IP infusion.

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

**Table 10: FDA – Schedule of Events, Year 2**

|                                          | W48<br>Dosing<br>Visit <sup>a</sup> | Start<br>Steroid<br>s                 | Follow-up Period                         |                               |             |             |             |                       |             |           |          |           |          |          |
|------------------------------------------|-------------------------------------|---------------------------------------|------------------------------------------|-------------------------------|-------------|-------------|-------------|-----------------------|-------------|-----------|----------|-----------|----------|----------|
| EW Visit Time<br>(Day/Week) <sup>b</sup> |                                     | D337–<br>D338<br>(+7)<br>Pre-<br>dose | D337–<br>D338 (+7)<br>Dose/Pos<br>t-dose | D352<br>Start<br>Steroid<br>s | W52         | W53         | W54         | Weekly<br>W55–<br>W59 | W60         | W72       | W7<br>8  | W84       | W9<br>0  | W9<br>6  |
| EW Visit Window<br>(Days)                |                                     | Pre-<br>dose                          | Dose/<br>Post-<br>dose                   | –                             | ±3          | ±3          | ±3          | ±3                    | ±3          | ±14       | ±14      | ±14       | ±14      | +7       |
| Visit Type                               |                                     | InPt                                  | InPt <sup>c</sup>                        | Phone                         | OPt/HH<br>d | OPt/HH<br>d | OPt/HH<br>d | OPt/HH<br>d           | OPt/HH<br>d | Phon<br>e | InP<br>t | Phon<br>e | InP<br>t | InP<br>t |
| Height <sup>e</sup>                      |                                     | X                                     |                                          |                               |             |             |             |                       |             |           |          |           | X        | X        |
| Weight                                   |                                     | X                                     | X                                        |                               | X           |             | X           |                       | X           | X         |          |           | X        |          |

|                                                                                                                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---------------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant concomitant medications                                                                                                | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Review eligibility criteria <sup>f</sup>                                                                                        | X |   |   |   |   |   |   |   |   |   |   |   |   |
| Dispense/administer oral prednisolone/placebo kit <sup>c</sup>                                                                  |   | X |   |   |   |   |   |   |   |   | X |   |   |
| Collect oral prednisolone/placebo kit                                                                                           |   |   |   |   |   |   |   |   |   |   |   | X |   |
| Prednisolone/placebo monitoring phone call (Refer to Table 14)                                                                  |   |   | X |   |   |   |   |   |   |   |   |   |   |
| Early morning cortisol and ACTH (24 hours after completing the prednisolone/placebo taper; abnormal levels reviewed by the CIC) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| GSD FAD eDiary <sup>h</sup>                                                                                                     |   | X |   |   |   |   |   | X |   |   |   |   |   |
| GSD FAD (weekly version) <sup>h</sup>                                                                                           |   |   |   |   |   |   |   | X |   |   |   |   |   |
| PGIS <sup>h</sup>                                                                                                               | X | X |   |   |   |   |   | X |   |   | X |   |   |
| PGIC <sup>h</sup>                                                                                                               | X | X |   |   |   |   |   | X |   |   | X |   |   |
| PGIC-CTT <sup>h</sup>                                                                                                           |   |   |   |   |   |   |   | X |   |   | X |   |   |
| EQ-5D-5L / EQ-5D-γ <sup>i</sup>                                                                                                 | X |   |   |   |   |   |   | X |   |   | X |   |   |
| HEOR assessments                                                                                                                | X |   |   |   |   |   |   |   |   | X | X |   |   |
| AEs/SAEs                                                                                                                        | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital sign measurements <sup>j</sup>                                                                                            | X | X |   | X | X | X | X | X | X | X | X | X | X |
| Complete physical examination <sup>k</sup>                                                                                      | X | X |   |   |   |   |   |   |   |   |   |   |   |

|                                                                                                                                      |   |   |  |   |   |   |   |   |   |   |   |   |  |
|--------------------------------------------------------------------------------------------------------------------------------------|---|---|--|---|---|---|---|---|---|---|---|---|--|
| Targeted physical examination <sup>k</sup>                                                                                           |   | X |  |   |   |   |   | X |   |   | X |   |  |
| 12-lead ECG                                                                                                                          | X |   |  |   |   |   |   |   |   |   | X |   |  |
| Urine pregnancy test (women of childbearing potential only)                                                                          |   |   |  | X | X |   |   | X | X | X | X | X |  |
| Standard clinical chemistry panel – Central Lab <sup>l</sup>                                                                         | X | X |  | X | X | X | X | X | X | X | X | X |  |
| Lactate <sup>m</sup>                                                                                                                 |   | X |  | X |   |   |   | X |   |   |   |   |  |
| Standard clinical chemistry panel – Local Lab <sup>m</sup>                                                                           |   | X |  |   |   |   |   | X |   | X | X |   |  |
| STAT glucose and lactate during CFC <sup>n</sup>                                                                                     | X |   |  |   |   |   |   | X |   |   | X |   |  |
| Cortisol and other HPA axis tests as needed <sup>o</sup>                                                                             |   |   |  |   |   |   |   |   |   | X | X |   |  |
| Cortisol, ACTH, free fatty acids, glucagon, insulin, C-peptide, growth hormone, IGFBP1, alanine, and ketones during CFC <sup>n</sup> | X |   |  |   |   |   |   | X |   |   | X |   |  |
| Hematology, coagulation panel, urinalysis – Central Lab                                                                              | X |   |  | X |   | X |   | X | X | X | X | X |  |
| 24-hour urine collection <sup>p</sup>                                                                                                | X |   |  |   |   |   |   | X |   |   |   |   |  |
| AAV8 binding antibody IgG testing (b) (4)                                                                                            | X | X |  |   |   | X |   | X |   | X | X |   |  |
| Cell-mediated immune response to G6Pase (ELISpot)                                                                                    | X |   |  |   |   | X |   | X |   |   |   |   |  |

|                                                                        |   |   |  |  |  |   |  |   |   |   |   |   |  |
|------------------------------------------------------------------------|---|---|--|--|--|---|--|---|---|---|---|---|--|
| Anti-G6Pase antibody assay                                             | X |   |  |  |  |   |  | X |   |   | X |   |  |
| Complement activity (C3, C4, SC5b-9, CH50, AH50, MBL) <sub>r</sub>     | X |   |  |  |  |   |  |   |   |   |   |   |  |
| Serum tryptase <sub>r</sub>                                            | X |   |  |  |  |   |  |   |   |   |   |   |  |
| Optional future research sample <sub>r</sub>                           |   | X |  |  |  | X |  | X |   |   | X |   |  |
| Liver ultrasound <sub>s</sub>                                          | X |   |  |  |  |   |  | X |   |   |   |   |  |
| SMBG <sup>t</sup>                                                      | X | X |  |  |  | X |  | X | X | X | X | X |  |
| CGM <sup>u</sup>                                                       | X | X |  |  |  | X |  | X | X | X | X | X |  |
| Assessment of prescribed cornstarch and cornstarch intake <sup>v</sup> | X | X |  |  |  | X |  | X | X | X | X | X |  |
| Assessment of prescribed diet and dietary intake <sup>v</sup>          | X | X |  |  |  | X |  | X | X | X | X | X |  |
| Controlled fasting challenge <sup>w</sup>                              | X |   |  |  |  |   |  | X |   |   | X |   |  |
| CFC Questionnaire <sup>w</sup>                                         | X |   |  |  |  |   |  | X |   |   | X |   |  |
| Subject exit interviews                                                |   |   |  |  |  |   |  | X |   |   | X |   |  |
| Premedication <sup>x</sup>                                             | X |   |  |  |  |   |  |   |   |   |   |   |  |
| IP infusion                                                            |   | X |  |  |  |   |  |   |   |   |   |   |  |

Source: Table 4 in Clinical protocol of Study DTX401-CL301 submitted in Module 5 of the BLA submission, Pages 27-31

a The Week 48 Visit cannot occur earlier than 48 weeks after the Day 1 IP administration.

b The timing of all Year 2 visits and assessments should be anchored to the date of the Week 48 dosing visit. For eg, the Week 60 visit is due to occur 12 weeks following administration of second blinded IP infusion in Year 2.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 8.1.1.2 Eligibility Criteria

Eligible subjects were ≥8 years old with a confirmed diagnosis of GSDIa by deficient G6Pase activity (on liver biopsy), or by molecular testing of *G6PC* gene. All subjects were receiving a therapeutic regimen of cornstarch with optimized and stable nutrition, glycemic and clinical status. Subjects with pre-existing antibodies to the AAV8 capsid, a history of specified hepatic conditions/dysfunction, or non-fasting triglycerides ≥1000 mg/dL were not eligible for dosing.

#### The FDA's Assessment:

##### *Major Inclusion Criteria*

1. Male and female patients ≥ 8 years of age at time of informed consent or assent.
2. Subject has a diagnosis of GSDIa confirmed by deficient enzymatic activity (on liver biopsy), or by molecular testing of *G6PC* gene revealing 2 pathogenic mutations. In the case where only a single pathogenic mutation is identified, clinical diagnosis is compatible with GSDIa and absence of characteristic features of GSDIb (ie, chronic neutropenia, inflammatory bowel disease).

##### *Clinical Comment*

GSDIa is an autosomal recessive disorder caused by biallelic pathogenic variants in the *G6PC1* gene. Diagnosis can be confirmed either by identifying two pathogenic mutations on molecular testing or by demonstrating absent or severely reduced G6Pase enzymatic activity on liver biopsy, a direct measure of the underlying functional deficiency. When only a single pathogenic variant is identified, a clinical diagnosis of GSDIa remains acceptable for enrollment, provided the patient's presentation is compatible with GSDIa and lacks the hallmark features of GSDIb, namely chronic neutropenia and inflammatory bowel disease.

3. Subject is currently receiving a therapeutic regimen of cornstarch (or equivalent), following international guidance/recommendations with stable nutrition, glycemic, and clinical status, as evidenced by:
  - No more than a 10% variation in weekly average daily cornstarch (or equivalent) intake over the last 4 weeks.
  - No more than a 25% variation in weekly average daily non-cornstarch carbohydrate over the last 4 weeks.
  - No more than 15% variation in weekly percentage of values in the target blood glucose range (60-120 mg/dL) over the last 4 weeks as measured by CGM and corroborated by SMBG. If adequate corroboration is not observed, this assessment should be made by SMBG.
  - No hospitalization for hypoglycemia and no severe hypoglycemic event (SHE) during the 4-week period preceding randomization and dosing, notwithstanding events of hypoglycemia due to unavoidable and unforeseeable events (e.g., infection, trauma) that transiently prevent the subject from tolerating enteral intake or acutely change the subject's

metabolic demands, provided that the subject quickly returns to their prior physiologic state.

*Clinical Comment*

Pre-randomization nutritional optimization and glycemic stability help attribute observed effects to DTX401 rather than improved disease management, while protecting placebo subjects from hypoglycemia risk.

However, restricting enrollment to patients already stable on cornstarch therapy raises questions about the true magnitude of unmet need and may underestimate DTX401's clinical benefit in the GSDIa population, where suboptimal glycemic control and frequent hypoglycemic episodes continue to represent a substantial burden.

*Major Exclusion Criteria*

- Detectable pre-existing antibodies to the AAV8 capsid during Screening.
- History of liver transplant, including hepatocyte cell therapy/transplant.
- History of severe hepatic fibrosis or cirrhosis as evidenced by any of the following: portal hypertension, ascites, splenomegaly, esophageal varices, hepatic encephalopathy, or a liver biopsy with evidence of stage III fibrosis.

*Clinical Comment*

Severe fibrosis (Stage III) is contraindicated in the USPI because advanced hepatic scarring reduces viable hepatocytes available for AAV8 transduction and transgene expression, while the hepatic inflammation inherent to AAV-based therapy poses an unacceptable risk of acute liver decompensation in an already compromised liver.

4. Presence of liver adenoma > 5 cm in size or presence of liver adenoma > 3 cm and ≤ 5 cm in size with a documented annual growth rate of ≥ 0.5 cm per year.

*Clinical Comment*

Patients with GSDIa lack functional G6Pase, leading to chronic pathological accumulation of glycogen and fat within hepatocytes and an intrinsic risk of hepatocellular adenoma formation. Excluding patients with large or rapidly growing adenomas (>5 cm, or >3 cm with growth ≥0.5 cm/year) safeguards the study population, given the elevated risk of malignant transformation to hepatocellular carcinoma in these lesions.

5. Significant hepatic injury or dysfunction as evidenced by imaging or any of the following laboratory abnormalities from 2 consecutive samples (collected at least 4 weeks apart).
  - ALT or aspartate aminotransferase > 2.5 × the upper limit of normal (ULN)
  - Total bilirubin > ULN unless the subject has Gilbert syndrome
  - Alkaline phosphatase > ULN, with gamma-glutamyl transferase > ULN

### *Clinical Comment*

This exclusion criterion safeguards the study population from the hepatotoxic risks associated with AAV-based gene therapy administration.

## 6. Non-fasting triglycerides $\geq$ 1000 mg/dL

### 8.1.1.3 Study Endpoints

Selection of Phase 3 study endpoints was informed by Health Authority guidance, clinical outcomes in Phase 1/2 studies 401GSDIA01 and 401GSDIA02, published literature, patient concept elicitation interviews, patient and caregiver surveys, Sponsor advisory boards, and FDA-sponsored patient and caregiver listening sessions.

#### **Primary Endpoint**

Percent change from Baseline to Week 48 in daily cornstarch intake for the DTX401 vs Placebo groups was the primary endpoint. Cornstarch reduction was selected as the primary endpoint following extensive patient-focused research—including FDA-sponsored patient and caregiver listening sessions, surveys, and interviews—which consistently identified the cornstarch regimen as one of the most burdensome aspects of GSDIa and a top priority for needing improvement. Across patient/caregiver listening sessions, advisory boards, and Phase 1/2 trial interviews, patients and caregivers emphasized the need for substantial reductions in cornstarch intake to improve quality of life while maintaining glycemic control. These converging data demonstrated that meaningful decreases in cornstarch use (often viewed as  $\geq 50\%$ ) represent a clinically important and patient-valued treatment benefit.

Cornstarch was assessed primarily by daily cornstarch intake (as reported by the subject on an e-diary over 4 weeks leading up to Baseline/Week 48 study visits and 7 days leading up to other study visits) and supported by prescribed cornstarch to demonstrate compliance with prescriptions (reported by treating clinical team on electronic data capture [EDC]).

#### **Secondary Endpoints**

Secondary endpoints subject to multiplicity include:

- Change from Baseline to Week 48 in total daily doses of cornstarch
- Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range ( $<70$  mg/dL), assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority
- Patient Global Impression of Change (PGIC) assessment score at Week 48

Other secondary efficacy endpoints include:

- Change from Baseline to Week 48 in time to hypoglycemia ( $<54$  mg/dL) during the controlled fasting challenge (CFC)
- Change from Baseline to Week 48 in percentage of glucose values in the range of 70-120 mg/dL, assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority

Secondary endpoints evaluated important aspects of GSDIa treatment and underlying disease including change in frequency of cornstarch dosing, glycemic control, fasting tolerance and subjects' experience of disease to provide supportive evidence of the appropriateness of cornstarch reductions assessed in the primary endpoint. Avoiding hypoglycemia and maintaining euglycemia are key goals in GSDIa management, and in Study DTX401-CL301 these measures were assessed by continuous glucose monitoring (CGM) to ensure cornstarch could be safely reduced after nutritional optimization and blinded dosing. Because patients were optimized at baseline, the study was designed to test non-inferiority in glycemic control, with DTX401 considered effective if it enabled meaningful cornstarch reduction while maintaining stable glucose levels. The non-inferiority margins were prespecified based on FDA guidance, published CGM data, observational study results, and expert clinical judgment. Primary analyses of glycemic control were performed using all available CGM data from the 4 weeks leading up to defined study visits assessing the change in percentage of glucose values in the hypoglycemic (< 70 mg/dL), severe hypoglycemic (<54 mg/dL) and euglycemic (70-120 mg/dL) ranges and supported by additional analysis of CGM. In the study, subjects were blinded to their CGM devices up to Week 96, including blinding to CGM values and CGM alarms. Investigators were unblinded to CGM values (as of protocol amendment 2) to ensure appropriate oversight, safety and to allow for objective adjustments of cornstarch to be made based on protocol defined glycemic threshold recommendations.

#### The FDA's Assessment:

##### **Primary Efficacy Endpoint**

##### *Percent Change From Baseline to Week 48 in Daily Cornstarch Intake for the DTX401 Group Compared With the Placebo Group*

The primary endpoint was derived from subject-reported data in an eDiary. Baseline was calculated as the average daily cornstarch intake over the four weeks prior to the Day 0 visit. For the primary efficacy analysis, data from Weeks 24, 30, 36, 42, and 48 were used, with intake averaged over one week prior to each visit, except for the Week 48 visit, which used a four-week average.

The primary analysis used actual cornstarch intake, and a supplementary analysis of prescribed cornstarch was planned to assess consistency between actual and prescribed cornstarch.

Cornstarch (CS) and dietary modifications were protocol-defined and prescribed by the Investigator. Cornstarch dosage modifications were based primarily on the subject's CGM trends over the preceding 7 days from the prior 4 weeks.

Guidelines for adjustment to the cornstarch prescription were used by investigators as follows:

- Decrease cornstarch intake by a target of 10% if glucose levels are repeatedly high (peaks  $\geq 110$  mg/dL and lows  $\geq 80$  mg/dL) for more than 15% of the time compared to the previous dose for at least 3 days in a 1-week period.
- Increase cornstarch intake by a target of 10% if glucose levels are low (peaks  $< 90$  mg/dL and lows  $< 60$  mg/dL) for more than 15% of the time compared to the previous dose for at least 3 days in a 1-week period.

#### *CGM Measurement*

- **Device:** Dexcom G6 CGM device CGM system provided by the study site
- Measured continuous interstitial glucose levels; data uploaded via study-issued laptop to a central database
- Weekly CGM reports were shared with the Investigator (subjects were **blinded** to their own CGM data until Week 96)
- During the CFC, a second real-time CGM device could be added at the Investigator's discretion for safety

#### *CGM Wear Duration*

- **Recommended:** Continuous wear throughout the entire study (Screening through Week 144/EOS)
- **Minimum required:** At least 4 consecutive weeks of wear prior to each key visit (Weeks 24, 30, 36, 42, 48, 72, 78, 84, 90, 96, 108, 120, 132, and 144/EOS)

#### *SMBG Frequency*

- **Recommended:** At least 4 measurements/day (morning, before two main meals/cornstarch doses, bedtime)
- **Minimum required:** At least 4 times/day for 4 weeks before Baseline, and 4 times/day for 1 week before each key scheduled visit
- **Additional SMBG** required when symptomatic or at Investigator's discretion
- Reasons for SMBG only needed to be recorded in the eDiary **if symptomatic**

#### *CDRH Consultation for GCM Use*

The clinical team requested CDRH's expert consultation on the use of the Dexcom G6 Continuous Glucose Monitor (CGM) as a measurement tool in the Phase 3 clinical study (DTX401-CL301) for DTX401. Please refer to Section [9](#) for details.

#### *Clinical Comment*

In past communications with the Sponsor (Table 3 in Section [3.2](#)), the FDA expressed concern with the use of reduction in cornstarch intake as a sole primary endpoint in a registrational study and recommended co-primary endpoints of cornstarch reduction and a metabolic measure such as TTH during CFC.

FDA considered that a reduction in the number of daily cornstarch doses is more relevant to improvements in quality of life. This is distinct from the percent reduction in CS intake, which measures the quantity of cornstarch consumed rather than the frequency of dosing, a distinction that matters because patient burden is driven primarily by how often patients must dose. This determination was supported by three FDA-requested patient listening sessions, in which patients and families consistently highlighted the burden of "living by the clock" due to frequent cornstarch dosing.

FDA noted that cornstarch intake, whether measured as percent reduction in total intake or reduction in daily doses, is a surrogate endpoint, not a direct measure of how patients feel, function, or survive. Both measures reflect investigator-prescribed dosing adjustments guided by CGM data rather than patient-reported outcomes, and therefore may predict, but do not directly demonstrate, clinical benefit.

### **Key Secondary Endpoints (Subject to Multiplicity)**

- Change from Baseline to Week 48 in number of total daily doses of cornstarch

This endpoint was derived from subject-reported eDiary data. The cornstarch regimen was prescribed and adjusted by investigators based primarily on CGM measures, as described above.

- Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (<70mg/dL [3.9 mmol/L]), assessed for non-inferiority; if non-inferiority is established, the endpoint will be tested for superiority.

The percentage of CGM glucose values in the hypoglycemic range (<70 mg/dL [3.9 mmol/L]) was assessed using blinded CGM data. The applicant justified this secondary endpoint on the basis that potential G6Pase enzyme restoration by DTX401 would be demonstrated by reductions in cornstarch intake while maintaining glycemic control, together may reflect improved overall metabolic control. This is clinically relevant because, in the absence of functional G6Pase, blood glucose levels below 70 mg/dL cannot be corrected through glycogenolysis; glucose-6-phosphate is instead shunted into alternative metabolic pathways, resulting in metabolic complications including lactic acidosis, hyperuricemia, and hypertriglyceridemia.

#### *Clinical Comment*

The sponsor proposed a 10% non-inferiority margin using a simulation-based method informed by historical data and Key Opinion Leader (KOL) input; KOLs advised that a difference of this magnitude would represent acceptable glycemic stability between treatment groups. While FDA acknowledges that the M1 estimation framework could not be applied due to the absence of placebo-controlled cornstarch trials in GSD Ia, the pre-specified 10% non-inferiority margin lacks a rigorous justification. Accordingly, the FDA review team elected to present the observed values.

- Change from Baseline to Week 48 on Patient Global Impression of Change (PGIC)

The PGIC is a single-item, self-reported measure that asks subjects to rate the overall change in their GSD Ia since the start of the study, using a 7-point response scale ranging from "much improved" (+3), moderately improved (+2), minimally improved (=1), no change (0), minimally worse (-1), moderately worse (-2), to "much worse" (-3). In pediatric subjects (ages 8–17), the item stem was adapted for age-appropriate comprehension. The instrument was completed electronically via the eDiary on the day before each applicable study visit. Both adult and pediatric versions were administered once during screening and at post-baseline visits.

*Clinical Comment*

The PGIC has several limitations that constrain its use as a regulatory endpoint. Its retrospective nature renders it vulnerable to recall bias, and as a generic single-item instrument, it collapses multiple distinct health domains into a single rating, limiting its clinical interpretability for a complex, multisystem disease like GSD Ia.

**Other Secondary Endpoint (Not Subject to Multiplicity)**

- Change from Baseline to Week 48 in time to hypoglycemia (<54 mg/dL [3.0 mmol/L]) during the CFC. This was based on venous blood glucose values collected in local lab data.

The CFC is a standardized, inpatient provocative metabolic assessment used to evaluate the capacity of GSDIa patients to maintain euglycemia during a period of fasting, serving as a direct functional proxy for hepatic glucose-6-phosphatase (G6Pase) activity. Improved fasting tolerance is a clinically meaningful outcome that directly addresses the core burden of GSDIa, where a single missed cornstarch dose can precipitate life-threatening hypoglycemia.

The CFC requires 24-hour inpatient admission. Subjects were to consume a personalized dinner followed by an oral cornstarch dose per their current prescription (within 3 hours of dinner), then fasting commenced. The fast was terminated upon glucose falling below 54 mg/dL, onset of clinical hypoglycemia symptoms, or completion of 15 hours without hypoglycemia. Glucose was monitored continuously via CGM, with capillary and STAT plasma glucose/lactate collected hourly, increasing to every 30 minutes once glucose reached ≤ 70 mg/dL.

*Clinical Comment*

During the BLA review, the FDA clinical team asked how the study captured the precise timing of hypoglycemia (defined as venous glucose < 54 mg/dL), given that blood samples were drawn at minimum 30-minute intervals. The Sponsor clarified that TTH was defined as the duration from the start of the fasting

challenge to the time the hypoglycemia threshold was reached. Investigators were not restricted to the 30-minute sampling schedule and could draw blood at any time if hypoglycemia was suspected based on clinical signs, symptoms, capillary glucose, or CGM readings. An additional unblinded CGM device was also available during fasting challenges to enable more precise, real-time glucose monitoring. However, the official end time of the fasting challenge was always determined by venous blood glucose sampling, not CGM readings.

- 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

As stated previously, while FDA acknowledges that the standard M1 estimation framework could not be applied given the absence of placebo-controlled cornstarch trials in GSD1a, the sponsor's justification does not meet the standard established in FDA's non-inferiority guidance. Therefore, the review team determined to present the observed values.

### **Tertiary Endpoint**

Metabolic control (based on observational data) from baseline to Week 48, and week 96:

- Pre-CFC triglyceride
- Pre-CFC whole blood lactate
- Pre-CFC plasma uric acid

#### **8.1.1.4 Statistical Analysis Plan and Amendments**

##### The Applicant's Description:

The original Statistical Analysis Plan (SAP) (v1.0) was finalized on 05 April 2024, prior to the database lock and primary efficacy analysis at Week 48.

A total sample size of 50 subjects (25 per group) was estimated to provide approximately 91% power to detect a difference in cornstarch reduction between DTX401 and placebo at Week 48 using a mixed model for repeated measures (MMRM) approach, based on assumptions of  $\geq 50\%$  reduction in the DTX401 group versus  $\leq 10\%$  in placebo and conservative estimates for variability, correlation, and discontinuation. These assumptions were informed by results from the Phase 1/2 study, and power was estimated by simulating 1000 datasets using Ultragenyx SAS code, identifying 50 subjects as sufficient to achieve  $\geq 90\%$  power for the primary endpoint.

The mixed model for repeated measures (MMRM) based on all observed data at Week 24 through Week 48 was used to analyze the primary, key secondary and other continuous efficacy endpoints. The MMRM included fixed effect of treatment group, visit, and treatment group-by-visit interaction, the stratification factors and baseline measurement as covariates. Efficacy analyses were based on the modified intention-to-

treat (mITT) Analysis Set and safety analyses were based on the Safety Analysis Set (defined in Section [8.1.1.6.3](#)).

The overall type I error rate for testing primary and key secondary endpoints was controlled at the 2-sided 0.05 alpha level. If the primary endpoint was met, the 3 key secondary endpoints were tested using the Hochberg method based on the rank order of the 2-sided p-values (defined in the SAP provided in Appendix 16.1.9 of the DTX401-CL301 Week 96 Clinical Study Report [CSR]).

The primary analysis for the study was performed after the last subject completed the PEAP (Week 48) or an Early Withdrawal Visit. All analyses planned in the SAP were performed using all data from the PEAP and any available data beyond the PEAP at the time of primary database lock. All analyses planned in the SAP were also performed after the last subject completed their Week 96 visit. The final database lock and analyses are planned to occur after all subjects complete their Week 144 visit or Early Withdrawal visit.

#### The FDA's Assessment:

For efficacy and safety analyses, FDA focuses primarily on all-treated population, defined as all patients who received their assigned treatment.

Please refer to the statistical review memo for details on sample size determination and other statistical considerations.

A two-sided family-wise Type I error rate of 0.05 was maintained across the primary and key secondary endpoints.

### **8.1.1.5 Protocol Amendments**

#### The Applicant's Description:

The study protocol was amended 3 times. Briefly, the study was amended to implement risk minimization measures, reduce patient burden, and to align with health authority feedback regarding endpoints. These changes did not impact the integrity of the trial or the interpretation of the results. Further details on key changes in the respective amendments are included in Appendix 16.1.1 of the DTX401-CL301 Week 96 CSR.

#### The FDA's Assessment:

FDA concurs with the Applicant regarding protocol amendments.

### **8.1.1.6 Study Results**

#### **8.1.1.6.1 Compliance with Good Clinical Practices**

##### Data:

Good Clinical Practice audits were conducted at the following investigational sites:

- Site 101 (Principal Investigator Rebecca Riba-Wolman; 02MAR2022 to 04MAR2022)

- Site 102 (Principal Investigator Areeg El-Gharbawy; 11APR2023 to 12APR2023)
- Site 104 (Principal Investigator David Rodriguez-Buritica; 24AUG2021 to 26AUG2021)
- Site 108 (Principal Investigator Diva De Leon; 18JUL2023 to 19JUL2023)
- Site 110 (Principal Investigator Jose Abdenur; 13MAR2024 to 14MAR2024)
- Site 201 (Principal Investigator John Mitchell; 18OCT2022 to 20OCT2022)
- Site 301 (Principal Investigator Terry Derks; 12SEP2023 to 13SEP2023)
- Site 307 (Principal Investigator Paolo Gandullia; 26SEP2023 to 27SEP2023)
- Site 309 (Principal Investigator Maria Luz Couce Pico; 18OCT2023 to 19OCT2023)

The Applicant's Position:

Study DTX401-CL301 was designed, conducted, recorded, and reported in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The Investigators and Sponsor made every effort to ensure that the study was and is conducted in full conformance with those principles; current US FDA and EU regulations; ICH Good Clinical Practice (GCP) guidelines; and local ethical and regulatory requirements.

The FDA's Assessment:

FDA concurs with the Applicant's position on compliance with Good Clinical Practices. Refer to Section [4.1](#).

#### **8.1.1.6.2 Financial Disclosure**

The Applicant's Position:

All the principal investigators and sub-investigators participating in the study were assessed for financial disclosures as defined in 21 Code of Federal Regulations (CFR) Part 54, and none had disclosable financial interests.

The FDA's Assessment:

The Applicant has adequately assessed clinical investigators for any financial interest/arrangements. FDA concurs with the Applicant's assessment of financial disclosure for study investigators.

#### **8.1.1.6.3 Patient Disposition**

Data:

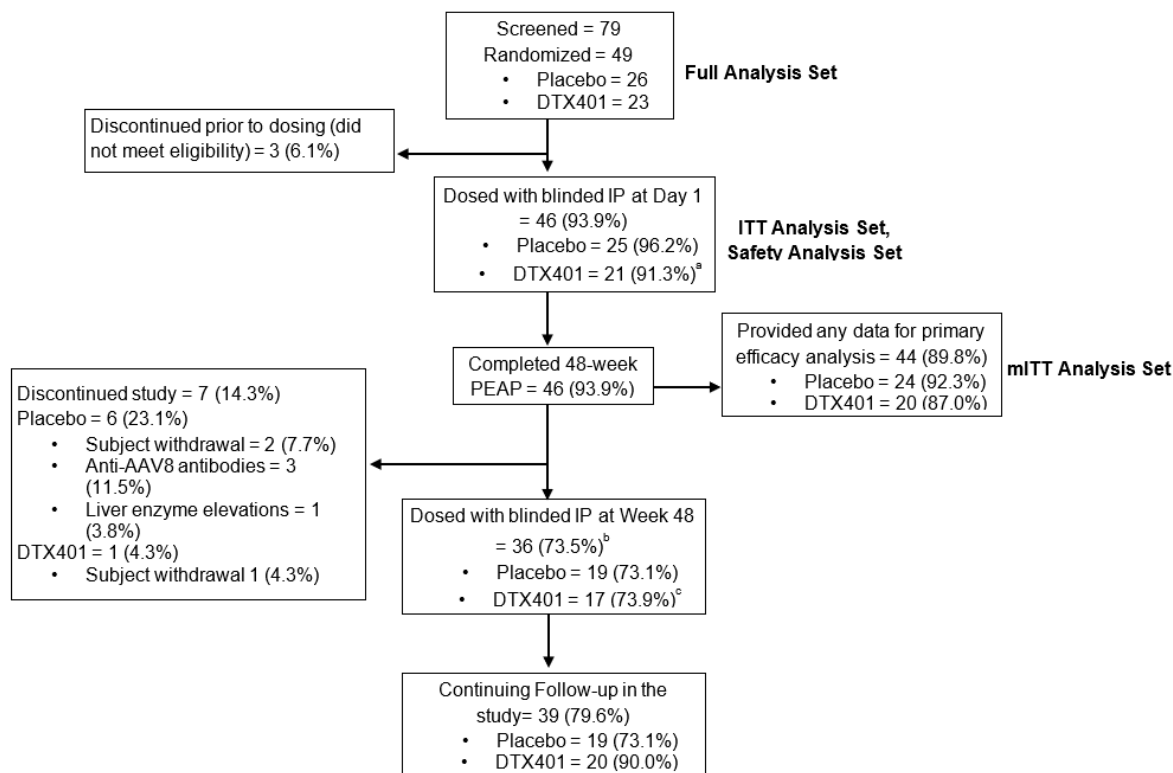
Subject disposition is shown in [Figure](#).

Applicant's Position:

Efficacy was evaluated in the mITT Analysis Set and was defined as all randomized subjects who were fully or partially dosed with IP and provided at least one post-dosing assessment pertaining to the primary efficacy analysis. The mITT Analysis Set

comprises 44 (89.8%) subjects, including 24 subjects from the Placebo group and 20 subjects from the DTX401 group. Safety was evaluated in the Safety Analysis Set and consists of all subjects treated with study IP, including subjects who received partial dose of IP. The Safety Analysis Set comprises 46 (93.9%) subjects.

**Figure 5: Applicant – Subject Disposition**



<sup>a</sup> Includes 2 subjects who were partially dosed.

<sup>b</sup> At Week 48, subjects in the Placebo group received DTX401 and subjects in the DTX401 group received placebo.

<sup>c</sup> Three subjects from the DTX401 group were not dosed with IP at Week 48, but continued follow-up in the study.

IP, investigational product; ITT, intention-to-treat; mITT, modified intention-to-treat; PEAP, Primary Efficacy Analysis Period

Source: DTX401-CL301 Week 96 CSR [Table 14.1.1.1](#), [Table 14.1.3.1.1](#), [Listing 16.2.1.1](#)

#### The FDA's Assessment:

Of 79 screened patients, 49 were enrolled and randomized; 46 (93.9%) received blinded investigational product at the Day 1 visit. The 3 who did not receive treatment were excluded at baseline due to unmet eligibility criteria, 2 for elevated non-fasting triglycerides and 1 for failure to meet stability criteria. Of the 46 treated patients, 2 (one DTX401, one placebo) had no post-dose efficacy data: one due to an infusion-related reaction and one due to withdrawal for personal reasons and study burden. The remaining 44 patients were included in Applicant's primary efficacy analysis (mITT).

For efficacy and safety analyses, FDA focuses primarily on all-treated population (N=46), defined as all patients who received their assigned treatment during PEAP. Some of the secondary endpoint analysis were based on mITT population (N=44).

#### 8.1.1.6.4 Protocol Violations/Deviations

##### Data:

During the PEAP, the most frequently reported major deviations in both treatment groups were in the “Study Procedures/Assessments” category, and mostly included labs not collected per protocol or deviations pertaining to the fasting challenge. This trend was consistent in the Crossover and Follow-up Periods.

##### The Applicant’s Position:

The protocol deviations did not impact study results or overall conclusions.

##### The FDA’s Assessment:

FDA concurs with the Applicant’s description and assessment of protocol deviations. The deviations that occurred during study conduct were reviewed and determined unlikely to impact the efficacy and safety analyses.

#### 8.1.1.6.5 Table of Demographic Characteristics

##### Data:

Subject demographics are presented in [Table](#).

**Table 11: Applicant – Subject Demographics (mITT Analysis Set)**

| <b>Parameter</b>            | <b>Placebo<br/>(N = 24)</b> | <b>DTX401<br/>(N = 20)</b> | <b>Total<br/>(N = 44)</b> |
|-----------------------------|-----------------------------|----------------------------|---------------------------|
| Age at consent (years)      |                             |                            |                           |
| Mean (SD)                   | 21.0 (8.5)                  | 20.7 (8.5)                 | 20.9 (8.4)                |
| Age group at consent, n (%) |                             |                            |                           |
| 8 – 17 years                | 9 (37.5)                    | 9 (45.0)                   | 18 (40.9)                 |
| ≥ 18 years                  | 15 (62.5)                   | 11 (55.0)                  | 26 (59.1)                 |
| Sex, n (%)                  |                             |                            |                           |
| Male                        | 12 (50.0)                   | 13 (65.0)                  | 25 (56.8)                 |
| Female                      | 12 (50.0)                   | 7 (35.0)                   | 19 (43.2)                 |
| Race, n (%)                 |                             |                            |                           |
| Asian                       | 2 (8.3)                     | 0                          | 2 (4.5)                   |
| White                       | 22 (91.7)                   | 17 (85.0)                  | 39 (88.6)                 |
| Not reported                | 0                           | 2 (10.0)                   | 2 (4.5)                   |
| Unknown                     |                             | 1 (5.0)                    | 1 (2.3)                   |
| Ethnicity, n (%)            |                             |                            |                           |
| Hispanic or Latino          | 3 (12.5)                    | 3 (15.0)                   | 6 (13.6)                  |
| Not Hispanic or Latino      | 16 (66.7)                   | 15 (75.0)                  | 31 (70.5)                 |

| <b>Parameter</b>                                                                    | <b>Placebo<br/>(N = 24)</b> | <b>DTX401<br/>(N = 20)</b> | <b>Total<br/>(N = 44)</b> |
|-------------------------------------------------------------------------------------|-----------------------------|----------------------------|---------------------------|
| Not Reported                                                                        | 5 (20.8)                    | 2 (10.0)                   | 7 (15.9)                  |
| Region, n (%)                                                                       |                             |                            |                           |
| North America                                                                       | 16 (66.7)                   | 12 (60.0)                  | 28 (63.6)                 |
| Europe                                                                              | 6 (25.0)                    | 6 (30.0)                   | 12 (27.3)                 |
| South America                                                                       | 2 (8.3)                     | 2 (10.0)                   | 4 (9.1)                   |
| Randomization stratification factors, n (%)                                         |                             |                            |                           |
| Age                                                                                 |                             |                            |                           |
| < 18 years                                                                          | 9 (37.5)                    | 9 (45.0)                   | 18 (40.9)                 |
| ≥ 18 years                                                                          | 15 (62.5)                   | 11 (55.0)                  | 26 (59.1)                 |
| Baseline percentage of values in target blood glucose range (60 – 120 mg/dL), n (%) |                             |                            |                           |
| < 60%                                                                               | 4 (16.7)                    | 5 (25.0)                   | 9 (20.5)                  |
| ≥ 60 % and ≤ 85%                                                                    | 15 (62.5)                   | 13 (65.0)                  | 28 (63.6)                 |
| > 85%                                                                               | 5 (20.8)                    | 2 (10.0)                   | 7 (15.9)                  |

Source: DTX401-CL301 Week 96 CSR [Table 14.1.2.1.2](#)

The Applicant's Position:

Demographics were generally balanced across the Placebo and DTX401 treatment groups.

The FDA's Assessment:

The demographic information and baseline disease characteristic information based on all-treated population (n=46) are shown in Table 12 and Table 13.

**Table 12: FDA – Demographic and Baseline Characteristics (N=46)**

| <b>Parameter</b>            | <b>Placebo (N=25)</b> | <b>DTX401 (N=21)</b> | <b>Total (N=46)</b> |
|-----------------------------|-----------------------|----------------------|---------------------|
| 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)             |

| Parameter                                                                           | Placebo (N=25) | DTX401 (N=21) | Total (N=46) |
|-------------------------------------------------------------------------------------|----------------|---------------|--------------|
| 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)     |

Source: Statistical reviewer and BLA 125858/0, Clinical Study Report-tfL, Table 14.1.2.1.1, p11

Abbreviations: CGM, Continuous Glucose Monitor; mITT, Modified Intention-to-Treat; SD, Standard Deviation

**Table 13: FDA – Medical History (N=46)**

| Parameter                                                           | Placebo (N=25) | DTX401 (N=21) | Total (N=46) |
|---------------------------------------------------------------------|----------------|---------------|--------------|
| <b>Age at diagnosis of GSDIa (years)</b>                            |                |               |              |
| Mean (SD)                                                           | 0.8 (1.8)      | 0.6 (1.3)     | 0.7 (1.6)    |
| <b>Ever taken uncooked cornstarch for management of GSDIa n (%)</b> |                |               |              |
| 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            |
| <b>Ever taken Glycosade for management of GSDIa - n (%)</b>         |                |               |              |
| Yes                                                                 | 19 (76.0)      | 17 (81.0)     | 36 (78.3)    |
| No                                                                  | 6 (24.0)       | 4 (19.0)      | 10 (21.7)    |
| <b>Currently taking Glycosade for management of GSDIa - n (%)</b>   |                |               |              |
| Yes                                                                 | 11 (44)        | 8 (38.1)      | 19 (41.3)    |
| No                                                                  | 8 (32.0)       | 8 (38.1)      | 16 (34.8)    |
| <b>Have ever used a feeding tube - n (%)</b>                        |                |               |              |
| Yes                                                                 | 18 (72.0)      | 15 (71.4)     | 33 (71.7)    |
| No                                                                  | 7 (28.0)       | 6 (28.6)      | 13 (28.3)    |
| <b>Currently use a feeding tube - n (%)</b>                         |                |               |              |
| Yes                                                                 | 4 (16.0)       | 6 (28.6)      | 10 (21.7)    |
| No                                                                  | 21 (84.0)      | 15 (71.4)     | 36 (78.3)    |

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

Abbreviations: Min, Minimum; Max, Maximum; n=Number is patients; SD, Standard deviation; SE, Standard error

Per Applicant's response to FDA IR,

- All study subjects included in the analysis dataset (N=46) screened negative (during the Screening window) for anti-AAV8 antibodies.
- At baseline, all 46 patients reported cornstarch intake (placebo: n=25; DTX401: n=21). Of these, 42 patients used uncooked cornstarch (placebo: n=23; DTX401: n=19) and 21 used Glycosade (placebo: n=11; DTX401: n=10). Seventeen patients used both uncooked cornstarch and Glycosade, which is consistent with the overlapping totals (42 + 21 - 17 = 46).

#### **8.1.1.6.6 Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)**

##### Data:

At Baseline, mean (SD) total daily cornstarch intake was 268.4 (110.0) g in the Placebo group and 294.1 (85.3) g in the DTX401 group. Mean (SD) number of daily doses of cornstarch at Baseline was 5.1 (1.4) in the Placebo group and 5.8 (1.4) in the DTX401 group, including 1.7 (1.2) and 1.7 (0.7) nighttime doses, respectively. The mean (SD) percentage of glucose values in the hypoglycemic range (< 70 mg/dL) was 1.95 (2.23) % in the Placebo group and 2.47 (2.56) % in the DTX401 group (median: 1.25% and 1.30%, respectively (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.1.1, 14.2.1.2.1.1, 14.2.1.3.1.1)).

Subjects in both groups reported a history of ER visits/hospitalization due to hypoglycemia, and a history of seizures (36.4%) and coma (18.2%) due to hypoglycemia. Subjects also reported a history of GSDIa-related metabolic, hepatic and renal conditions (hypertriglyceridemia [86.4%], hepatomegaly [88.6%], hepatic steatosis [43.2%], hepatic adenoma [27.3%]), and other comorbidities secondary to GSDIa (DTX401-CL301 Week 96 CSR Tables 14.1.2.2.2.2, 14.1.2.2.2.4).

##### The Applicant's Position:

At Baseline, subjects in both groups consumed similar large quantities of cornstarch to avoid hypoglycemia and manage their GSDIa. Consistent with the literature in GSDIa (Steunenberget al., 2018), high rates of hypoglycemia-related and disease-related complications were observed in both treatment groups. Percentage of glucose values in the hypoglycemic range (< 70 mg/dL) were mostly balanced across both groups at Baseline, following protocol-defined nutrition optimization and stabilization of all subjects during the Screening Period.

##### The FDA's Assessment:

FDA concurs with Applicant's position. Refer to FDA assessment in Section [8.1.1.6.5](#) above.

#### **8.1.1.6.7 Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

##### Data/The Applicant's Position:

DTX401 was administered as a single infusion in an inpatient setting by site personnel who documented any deviations in the case report form (CRF). During the PEAP, the infusion was terminated in 2 subjects (9.5%) in the DTX401 group with serious infusion-related reactions (IRRs) within 1 min and 6 min into the infusion, respectively. Compliance with the prophylactic immunomodulatory regimen was monitored through source data verification by Site Monitors against pharmacy records and subject progress notes.

### The FDA's Assessment:

All 46 patients in the mITT population received their assigned treatment and premedications prior to infusion. Two patients experienced anaphylactic/infusion-related reactions resulting in immediate discontinuation of the infusion; consequently, these patients did not receive a full dose of DTX401 and were not administered the corticosteroid regimen.

Among patients who received DTX401, 21 in the Primary Efficacy Analysis Period (PEAP) and 19 who crossed over from Placebo to DTX401 extended and repeated courses of corticosteroids (prednisolone) were administered, as summarized in Table 14.

The primary clinical indication in both groups was hepatic reaction, specifically non-serious transaminase elevations (ALT and/or AST), consistent with the anticipated immunogenic response to AAV-based gene therapy. Two patients in the Crossover group received prednisolone for one day beyond the protocol-specified duration, with no associated hepatic adverse events.

**Table 14: FDA – Extended or Repeated Corticosteroid Use (N=40)**

| <b>Parameter</b>                                                 | <b>PEAP<br/>DTX401<br/>N=21</b> | <b>Crossover Placebo→DTX401<br/>N=19</b> |
|------------------------------------------------------------------|---------------------------------|------------------------------------------|
| N Patients with extended/repeated prednisolone                   | 10                              | 12                                       |
| Total cycles across all patients                                 | 15                              | 15                                       |
| 1 Cycle, n                                                       | 5                               | 9                                        |
| 2 Cycles, n                                                      | 5                               | 3                                        |
| Total prednisolone dose range (mg)                               | 1,930–8,900                     | 1,975–4,772                              |
| Mean total prednisolone dose (mg)                                | ~4,110                          | ~3,010                                   |
| Duration range (days)                                            | 99–244                          | 59–170                                   |
| Mean duration (days)                                             | ~130                            | ~92                                      |
| Primary indication: hepatic reaction (transaminase elevation), n | 10 (100%)                       | 10 (83.3%)                               |
| No hepatic AE reported, n                                        | 0                               | 2 (16.7%) <sup>a</sup>                   |

Source: Clinical review team adapted from Applicant's response to clinical IR dated June 5/2026  
Abbreviation: AE, adverse event

### **8.1.1.6.8 Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**

#### **Primary Endpoint: Total Daily Cornstarch Intake**

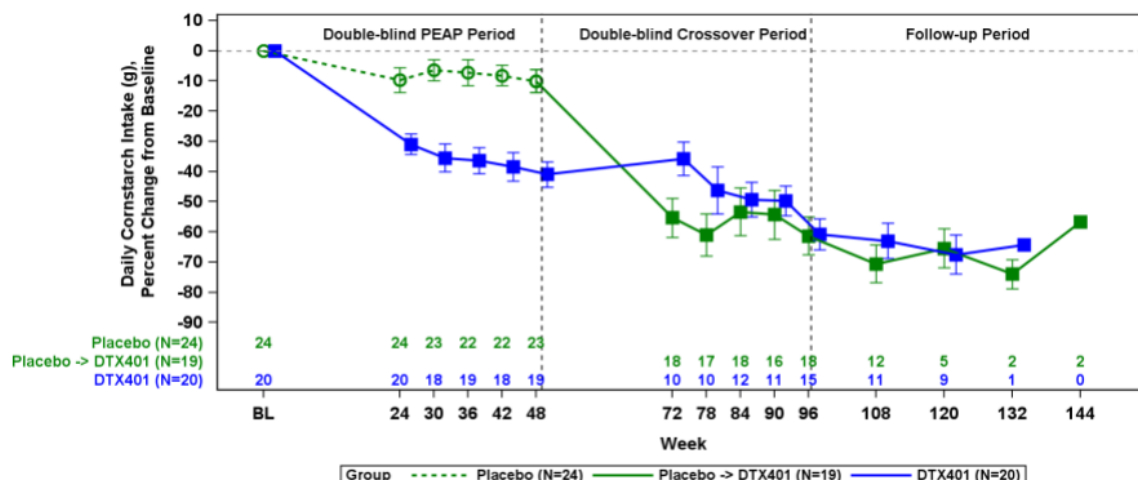
##### Data:

**PEAP:** The primary endpoint of the study was met. At Week 48, the least squares (LS) mean (SE) percent change from Baseline to Week 48 in total daily cornstarch intake was -10 (4.1) % in the Placebo group (n = 23) and vs -41 (4.6) % in the DTX401 group (n = 19) (least squares [LS] mean difference [SE]: -31 [5.7] %, p < 0.0001).

**Crossover Period:** In the Crossover Placebo→DTX401 group (n = 18), at 48 weeks after treatment with DTX401 (ie, Week 96), the mean (SD) percent change from Crossover Baseline in total daily cornstarch intake was -61 (26.8) %. At Week 96, mean (SD) percent change from Baseline was -61 (19.7) % in the DTX401 group.

**Follow-up Period:** At the last available visit for all subjects, the mean (SD) percent change from Crossover Baseline in total daily cornstarch intake was -64 (23.4) % in the Crossover Placebo→DTX401 group, and the mean (SD) percent change from Baseline in total daily cornstarch intake was -60 (20.7) % in the DTX401 group.

**Figure 6: Applicant – Percent Change from Baseline in Daily Cornstarch Intake (mITT Analysis Set)**



For the Crossover Placebo→DTX401 group, Baseline is the last observation prior to DTX401 dosing.

The number of subjects in each treatment group with available data at a given timepoint is shown along the X axis.

Above analysis includes all subject-reported cornstarch data. Data entry error on e-diary noted at Week 72 inconsistent with prescribed cornstarch for one subject in the DTX401 group.

BL, Baseline; mITT, modified intention-to-treat; PEAP, Primary Efficacy Analysis Period  
Source: DTX401-CL301 Week 96 CSR Figure 14.2.1.1.1.2

### Responder Analyses

Responder analyses were conducted using a pre-defined ( $\geq 50\%$ ) threshold for reduction from Baseline in cornstarch intake consistent with thresholds of clinical meaningfulness from trial patient interviews. At Week 48, 1/23 subjects (4.3%) in the Placebo group had  $\geq 50\%$  reduction in daily cornstarch intake compared with 7/19 subjects (36.8%) in the DTX401 group ( $p = 0.0038$ ). At 48 weeks after treatment with DTX401 (ie, Week 96) for the Crossover Placebo→DTX401 group, 13/18 subjects (72.2%) had  $\geq 50\%$  reduction, demonstrating a larger reduction as compared to the DTX401 group at Week 48 (ie, within the same timeframe post-dose). At Week 96, 10/15 subjects (66.7%) in the DTX401 group had  $\geq 50\%$  reduction, in line with the continued decline over time in cornstarch intake after the PEAP during the Crossover Period (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.8, 14.2.1.1.8.1).

### Sensitivity Analyses

Sensitivity analyses of the primary endpoint included assessment of daily cornstarch intake during the PEAP based on weeks where data is provided for at least 4 out of 7

days, sensitivity to missing data after imputing missing endpoint data by multiple imputation and sensitivity to intercurrent events eg illness, surgery, physiological changes, concomitant medication that could impact glycemic control. The number of subjects with intercurrent events was low (2 Placebo subjects, 3 DTX401 subjects). Results from all sensitivity analyses were consistent with the primary analysis (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.9, 14.2.1.1.13, 14.2.1.1.14).

### **Subgroup Analysis**

*Age (8 – 17 years and  $\geq 18$  years):* During the PEAP, at Week 48, the mean (SD) percent reduction in daily cornstarch intake was smaller for pediatric subjects compared with adults in the DTX401 group (35 [19.3] % vs -46 [17.0] %, respectively). In the Crossover Period, the mean (SD) percent change in cornstarch intake was slightly lower in pediatric vs adult subjects in the Crossover Placebo→DTX401 group (-55 [29.9] % and -64 [26.5] %, respectively). At 96 weeks after treatment in the DTX401 group, continued reductions in the mean (SD) percent change in cornstarch intake were observed for both pediatric and adult subjects (-68 [20.3] % and -57 [19.3] %, respectively). Cornstarch reductions for both age subgroups were substantially greater in the Crossover Placebo→DTX401 group than those observed for the Placebo and DTX401 groups during the PEAP at Week 48 (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.16.1, 14.2.1.1.16.2, 14.2.1.1.16.3, 14.2.1.1.16.4). Additional subgroup analyses are included in the DTX401-CL301 Week 96 CSR.

### **Additional/Supplementary Analyses**

*Nighttime cornstarch intake:* Nighttime cornstarch intake defined as any dose for which subjects reported they had to wake up from their sleep increased from Baseline to Week 48 in the Placebo group (mean [SD] percent change from Baseline: +21 [18.5] %) but statistically significantly reduced in the DTX401 group (mean [SD] percent change -39 [18.3] %). At 48 weeks after treatment with DTX401 (ie, Week 96) for the Crossover Placebo→DTX401 group, nighttime cornstarch intake markedly reduced from Crossover Baseline (mean [SD] percent change -75 [26.2] %). At Week 96, there was a further decline in nighttime cornstarch intake in the DTX401 group (mean [SD] percent change -70 [34.1] %). At Week 96, there was a further decline in nighttime cornstarch intake in the DTX401 group (mean [SD] percent change -70 [34.1] %) (DTX401-CL301 Week 96 CSR Tables 14.2.1.1.2.2.1, 14.2.1.2.2.2.2).

*Prescribed cornstarch intake:* The LS mean (SE) percent change from Baseline to Week 48 in total daily prescribed cornstarch was -9 (4.0) % in the Placebo group compared with -40 (4.4) % in the DTX401 group (LS mean difference [SE]: -31 [5.5] %,  $p < 0.0001$ ), which is highly consistent with the percent change from Baseline to Week 48 in total daily cornstarch intake (ie, the primary endpoint) (DTX401-CL301 Week 96 CSR Table 14.2.1.1.4).

*Compliance with prescribed cornstarch:* Non-compliance with daily cornstarch intake and prescribed cornstarch was assessed by Investigators at study visits and non-compliance was infrequent during the PEAP. At Week 48, 2 subjects in each treatment group were reported by the Principal Investigator to be noncompliant with prescribed cornstarch. The mean (SD) magnitude of non-compliance with prescribed cornstarch at

Week 48 was low and < 10% in both treatment groups (Placebo: 4 [5.3] % and DTX401: 8 [10.9] %) (DTX401-CL301 Week 96 CSR Table 14.1.5.1).

The Applicant's Position:

***DTX401 treatment resulted in statistically significant and clinically meaningful reductions in daily cornstarch intake compared to Placebo during the PEAP, with even greater reductions observed during the Crossover Period***

- DTX401 treatment resulted in a statistically significant reduction in cornstarch intake in the DTX401 group compared with Placebo group at Week 48, achieving the primary endpoint of the study.
- Greater reductions in total daily cornstarch intake in the Crossover Placebo→DTX401 group vs the DTX401 group during the PEAP and continued reductions in daily cornstarch intake in the DTX401 group after the PEAP suggest that the full magnitude of DTX401 treatment effect was not captured in the double-blind PEAP. During the Crossover Period, subjects and Investigators were aware they had all been dosed with DTX401 either at Day 1 or Week 48, which may have increased confidence for greater or more rapid reductions in cornstarch than the PEAP when they may have exercised more conservative treatment decisions.
- In both pediatric (8–17 years of age) and adult ( $\geq 18$  years) subgroups of subjects, significantly greater reductions in cornstarch were observed in the DTX401 group vs the Placebo group. In DTX401-treated subjects in the PEAP, pediatric subjects had lower reductions in cornstarch compared with adult subjects. Greater reductions in cornstarch were observed in both treatment groups in the Crossover Period.
- The appropriateness and clinical meaningfulness of cornstarch reductions following DTX401 treatment is supported by results on other key trial endpoints, patient experience research, direct patient feedback obtained via trial interviews, and mixed methods analysis using quantitative trial and interview data. See Section [8.1.4.1](#).
- Prescribed cornstarch was highly consistent with daily cornstarch intake with low rates of non-compliance demonstrating compliance and objectivity as investigators. adjusted cornstarch in line with protocol recommended glycemic thresholds in the study.
- The substantial reductions in nighttime cornstarch intake following DTX401 are particularly notable as patients and caregivers may be hesitant to alter nighttime cornstarch doses in fear of severe hypoglycemia while they are asleep. Reduction in nighttime cornstarch intake is meaningful to patients/caregivers as it has a positive impact on their sleep quality and overall disease burden.

The FDA's Assessment of Efficacy:

This section presents FDA's independent analysis of all efficacy outcomes from the Phase 3 study (DTX401-CL301), including the primary, key secondary, other secondary, and relevant tertiary endpoints.

The primary analysis population used for the FDA analyses include all patients who received their assigned treatment (n=46).

## Primary Endpoint

- Percent change from baseline (CFB) to Week 48 in daily cornstarch intake (grams)

The primary endpoint was derived from subject-reported data in an eDiary. The CS intake regimen was prescribed and adjusted weekly by the blinded investigator based on CGM measured, and was calculated as the average daily cornstarch intake over the four weeks prior to the Day 0 visit. For the primary efficacy analysis, data from Weeks 24, 30, 36, 42, and 48 were used, with intake averaged over one week prior to each visit, except for the Week 48 visit, which used a four-week average.

Based on the all-treated population (N=46; Table 15), the MMRM model estimated a least squares (LS) mean percent change from baseline to Week 48 in total daily cornstarch intake of -10.0% (SE: 3.6) in the placebo group and -41.0% (SE: 3.9) in the DTX401 group, yielding an LS mean difference of -30.9% (95% CI: -40.8%, -20.9%;  $p < 0.0001$ ). The results based on the all-randomized and per-protocol populations were similar (not presented).

**Table 15: FDA – Primary Efficacy Results: Percent Change From Baseline to Week 48 in Daily Cornstarch Intake (N=46)**

| Parameter              | DTX401 (N=21) | Placebo (N=25) | Difference [DTX401-Placebo] (95% CI; p-Value) |
|------------------------|---------------|----------------|-----------------------------------------------|
| Baseline (g) mean (SD) | 293.9 (83.2)  | 271.7 (109.0)  |                                               |
| % CFB LS Mean (SE)     | -41.1 (3.9)   | -10.2 (3.6)    | -30.9 (-40.8, -20.9), $p < 0.0001$            |

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

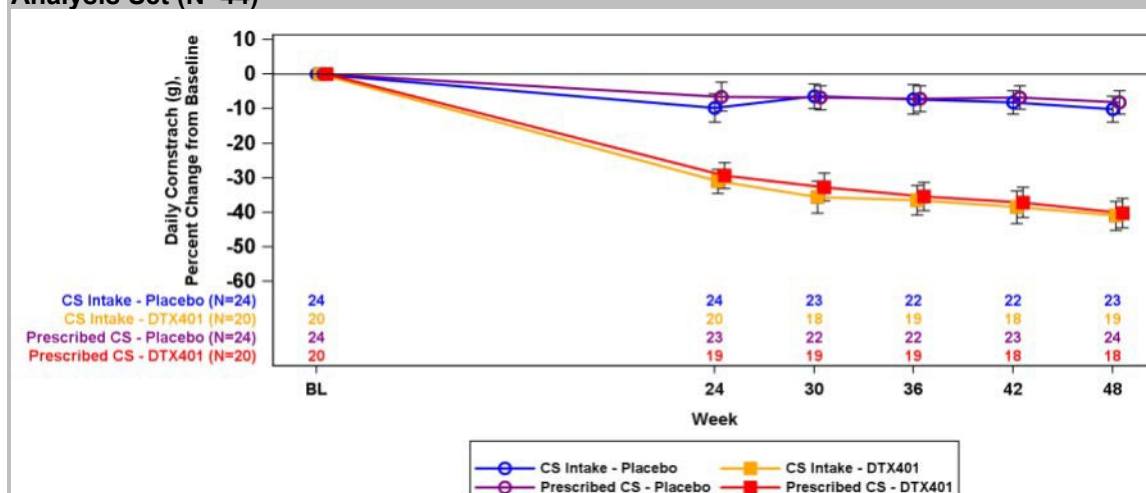
The LS Mean, LS Mean Difference, SE, 95% CI and 2-sided p-value are from MMRM (mixed-model for repeated measures) which includes percent change from baseline in daily cornstarch intake as the dependent variable, stratification factors, visit, treatment, and visit by treatment as fixed factors and adjusted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

Abbreviations: %CFB, Percent change from baseline; CI, Confidence interval; LS, Least square; SD, Standard deviation; SE, Standard error

### *Supplemental Analysis of Actual Versus Prescribed Cornstarch Use*

The comparison of percent change from Baseline in daily cornstarch intake during PEAP between actual cornstarch intake and prescribed cornstarch intake is shown in Figure 7. This analysis was based on the EES (N=44). The LS mean (SE) percent change from Baseline to Week 48 in total daily prescribed cornstarch was -9 (4.0) % in the Placebo and -40 (4.4) % in the DTX401 group (LS mean difference [SE]: -31 [5.5] %,  $p < 0.0001$ ). These findings align with the actual daily cornstarch intake reported by patients, indicating adherence to their prescribed regimens.

**Figure 7: FDA – Percent Change From Baseline in Daily Cornstarch Intake During PEAP, EES Analysis Set (N=44)**



Source: BLA 125858/0, Clinical Study Report, Figure 5, p84

The number of patients in each treatment group with available data at a given timepoint is shown along the X axis.

Abbreviations: BL, Baseline; CS, Cornstarch; mITT, Modified Intention-to-treat; PEAP, Primary Efficacy Analysis Period

The primary endpoint results demonstrate a statistically significant reduction in cornstarch intake in patients with GSD Ia during PEAP. The close alignment between prescribed and actual cornstarch intake suggests no meaningful discrepancy that would confound interpretation of these findings.

## Key Secondary Endpoints

- Change from Baseline to Week 48 in number of total daily doses of cornstarch

The analysis results based on all-treated are presented in Table 16. 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 16: FDA – Secondary Efficacy Results: Change From Baseline to Week 48 in Number of Daily CS Doses (N=46)**

| Parameter                | DTX401 (N=21) | Placebo (N=25) |
|--------------------------|---------------|----------------|
| Baseline                 |               |                |
| Mean (SD)                | 5.8 (1.4)     | 5.2 (1.4)      |
| Week 48                  |               |                |
| LS Mean (SE)             | -1.1 (0.2)    | -0.2 (0.2)     |
| 95% CI                   | (-1.5, -0.7)  | (-0.6, 0.1)    |
| LS Mean Difference (SE)* |               | -0.9 (0.3)     |
| 95% CI                   |               | (-1.4, -0.4)   |
| p value                  |               | 0.0004         |

Source: Statistical reviewer

\*Multiple imputation method was used for handling missing data.

Abbreviations: LS, Least Squares; mITT, Modified Intention-to-Treat; MMRM, Mixed-model for repeated measures

### Supplementary Analysis: Number of Nighttime Cornstarch Doses

The results of nighttime dose frequency at Week 48 are presented in Table 17. 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 17: FDA – Nighttime Dose Frequency (N=30)**

| 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       |             |

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

Abbreviations: CI, Confidence interval; mITT, Modified intent-to-treat; SD, Standard deviation; SE, Standard error

The 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. FDA statistical team 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 18](#), 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 18: FDA – Nighttime Dose Frequency Without Rounding (N=46)**

| 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) |             |

Source: Reviewer's summary

Abbreviations: CI, Confidence interval; SD, Standard deviation; SE, Standard error

FDA statistical team performed additional descriptive analyses on nighttime cornstarch use status change (Table 19). 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 19: FDA – Nighttime Cornstarch Usage Analysis at Week 48 and Week 96, All-Treated Population (N=46)**

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

Source: Statistical reviewer

<sup>a</sup> 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.

Abbreviation: mITT=Modified Intent-to-treat

DTX401 demonstrated a statistically significant reduction in total daily cornstarch doses, supporting a treatment benefit. However, the effect size is relatively modest (approximately one dose per day), and the supplementary nighttime analysis suggests that the impact of on one of the most burdensome aspects (e.g., nighttime dosing) was limited.

- Percentage of glucose values in hypoglycemic range (< 70 mg/dL)

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 mg/dL was 0.1% (0.8%) in the placebo group compared with 3.0% (0.9%) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: 2.9% [1.2%]).

**Table 20: FDA – Percent Time (%) in Range of Glucose Values < 70 mg/dL (N=46)**

| Weeks After Treatment     | DTX401 (N=21) | Placebo (N=25) |
|---------------------------|---------------|----------------|
| Baseline                  |               |                |
| n                         | 21            | 25             |
| Mean (SD)                 | 2.5 (2.5)     | 1.9 (2.2)      |
| MMRM estimates at Week 48 |               |                |
| LS Mean (SE)              | 3.0 (0.9)     | 0.1 (0.8)      |
| 95% CI                    | (1.2, 4.8)    | (-1.5, 1.8)    |
| LS mean difference (SE)   |               | 2.9 (1.2)      |
| 95% CI                    |               | (0.6, 5.2)     |

Source: Statistical reviewer

Note: Multiple imputation method was used for handling all missing data.

Abbreviations: LS, Least Squares; mITT, Modified Intention-to-Treat; MMRM, Mixed-model for repeated measures

### 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 21. At Week 48, the LS mean (SE) change from baseline in percentage of glucose values < 54 mg/dL was 0.2 (0.2) in the placebo group and 0.7% (0.3%) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo]: 0.51% [0.33%]; 95% CI [-0.15%, 1.16%]). At Week 48, the LS mean (SE) change from Baseline in percentage of glucose values > 120 mg/dL was 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 21: FDA – Percent Time (%) in Range of Glucose Values < 54 mg/dL and >120 mg/dL, mITT (N=44)**

| Parameter                                | < 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)                                | 0.21 (0.37)                | 0.33 (0.46)               | 36.84 (18.20)               | 34.18 (17.81)              |
| Week 48                                  |                            |                           |                             |                            |
| n                                        | 23                         | 19                        | 23                          | 19                         |
| Mean (SD)                                | 0.46 (0.66)                | 1.05 (1.47)               | 42.77 (14.29)               | 34.02 (18.94)              |
| Change from baseline, mean (SD)          | 0.24 (0.71)                | 0.78 (1.19)               | 6.37 (21.38)                | -0.22 (18.79)              |
| LS mean (SE)                             | 0.23 (0.23)                | 0.74 (0.26)               | 6.46 (3.06)                 | -2.75 (3.40)               |
| 95% CI                                   | (-0.23, 0.69)              | (0.22, 1.25)              | (0.39, 12.54)               | (-9.50, 4.00)              |
| LS mean difference (SE) [DTX401-Placebo] | 0.51 (0.33)                |                           | -9.21 (4.37)                |                            |
| 95% CI                                   | (-0.15, 1.16)              |                           | (-17.89, -0.54)             |                            |

Source: Statistical reviewer

Note: Multiple imputation method was used for handling all missing data.

Abbreviations: LS, Least Squares; mITT, Modified Intention-to-Treat; MMRM, Mixed-model for repeated measures; PEAP, Primary Efficacy Analysis Period

### • Patient Global Impression of Change (PGIC)

The analysis based on all-treated population is presented in Table 22. At Week 48, The LS mean (SE) difference (DTX401-Placebo) between the placebo group and the DTX401 group was 0.4 (0.4), p=0.2781.

**Table 22: FDA – PGIC (N=46)**

| MMRM Estimates at Week 48 | DTX401 (N=21) | Placebo (N=25) |
|---------------------------|---------------|----------------|
| LS mean (SE)              | 1.4 (0.3)     | 1.0 (0.3)      |
| 95% CI                    | (0.8, 2.0)    | (0.4, 1.5)     |
| LS mean difference (SE)   |               | 0.4 (0.4)      |
| 95% CI                    |               | (-0.4, 1.2)    |
| p-value                   |               | p=0.2781       |

Source: Statistical reviewer

Abbreviations: LS, Least Squares; mITT, Modified Intention-to-Treat; MMRM, Mixed-model for repeated measures; PEAP, Primary Efficacy Analysis Period

PGIC assessment is retrospective, single-item design is susceptible to recall bias and may not fully capture the complexity of a multisystem disease like GSD1a.

### Other Secondary Endpoints Analysis: Not Subject to Multiplicity

- Change from Baseline to Week 48 in time to hypoglycemia (<54 mg/dL [3.0 mmol/L]) during the CFC

The results for TTH during CFC are presented in Table 23. At baseline, the mean (SD) was 6.2 (3.1) hours in the placebo group and 7.1 (4.1) hours in the DTX401 group. 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 23: FDA – Time to Hypoglycemia (Hours) During Controlled Fasting Challenge at Week 48 (N=44)**

| Weeks After Treatment                    | Placebo       | DTX401        |
|------------------------------------------|---------------|---------------|
| Baseline                                 |               |               |
| n                                        | 24            | 20            |
| Mean (SD)                                | 6.18 (3.07)   | 7.10 (4.09)   |
| Week 36                                  |               |               |
| n                                        | 20            | 16            |
| Mean (SD)                                | 7.19 (3.82)   | 9.58 (5.07)   |
| Change from baseline, mean (SD)          | 0.65 (2.85)   | 1.84 (3.98)   |
| Week 48                                  |               |               |
| N                                        | 23            | 18            |
| Mean (SD)                                | 6.97 (3.68)   | 8.33 (4.88)   |
| Change from baseline, mean (SD)          | 0.68 (2.67)   | 1.00 (4.74)   |
| LS mean (SE)                             | 0.50 (0.80)   | 1.12 (0.91)   |
| 95% CI                                   | (-1.10, 2.11) | (-0.71, 2.95) |
| LS mean difference (SE) [DTX401-Placebo] | 0.61 (1.13)   |               |
| 95% CI                                   | (-1.66, 2.89) |               |
| p value                                  | 0.590         |               |

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

CI, Confidence interval; LS, Least squares; SD, Standard deviation; SE, Standard error

DTX401-treated patients demonstrated a numerically greater improvement in fasting tolerance relative to placebo, the between-group difference was small in magnitude (0.6 hours) and did not reach statistical significance. The modest numerical improvement may indicate partial restoration of G6Pase function,

particularly given that fasting tolerance was assessed in the context of already reduced cornstarch (CS) intake.

- Time in range of glucose values 70-120 mg/dL (N=44) is shown in Table 24.

The results of the change of percentage of Glucose Values in 70 – 120 mg/dL are presented in Table 24. At Week 48, the LS mean (SE) change from baseline in percentage of glucose values in the 70 – 120 mg/dL range was -6.54% (2.64%) in the placebo group and -0.51% (2.93%) in the DTX401 group (LS mean difference [SE] [DTX401-Placebo] was 6.03% [3.79%]; 95% CI: [-1.47%, 13.52%]).

**Table 24: FDA – Time in Range of Glucose Values 70-120 mg/dL (N=44)**

| Weeks After Treatment                    | Placebo (N=24)  | DTX401 (N=20) |
|------------------------------------------|-----------------|---------------|
| Baseline                                 |                 |               |
| n                                        | 24              | 20            |
| Mean (SD)                                | 61.21 (16.95)   | 63.38 (16.23) |
| Week 48                                  |                 |               |
| n                                        | 23              | 19            |
| Mean (SD)                                | 55.11 (13.92)   | 60.48 (14.32) |
| Change from baseline, mean (SD)          | -6.48 (20.23)   | -2.91 (16.79) |
| LS mean (SE)                             | -6.54 (2.64)    | -0.51 (2.93)  |
| 95% CI                                   | (-11.77, -1.31) | (-6.32, 5.29) |
| LS mean difference (SE) [DTX401-Placebo] | 6.03 (3.79)     |               |
| 95% CI                                   | (-1.47, 13.52)  |               |

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

Abbreviations: CI, Confidence Interval; LS, Least squares; SD, Standard deviation; SE, Standard error

### Tertiary Endpoint Analysis: Metabolic Control (Observational Data)

Lactate, uric acid, and triglycerides were assessed as part of the efficacy evaluation to examine the degree of metabolic control achieved during the study. Results are based on observed data and are presented in Table 25 below.

Across all three parameters, DTX401-treated groups trended toward greater elevations compared to Placebo, with the most pronounced differences observed for triglycerides. Although these analyses are observational, the findings suggest that the expected improvement in metabolic control was not demonstrated in the context of reduced cornstarch intake.

**Table 25: FDA – Pre-CFC Metabolic Parameters: PEAP and Crossover Periods**

| Parameter                | Placebo     | DTX401      | Placebo<br>→DTX401 |
|--------------------------|-------------|-------------|--------------------|
| Pre-CFC lactate (mmol/L) |             |             |                    |
| Baseline                 |             |             |                    |
| n                        | 24          | 18          | 19                 |
| Mean (SD)                | 2.69 (1.80) | 2.31 (1.23) | 3.29<br>(2.75)     |

| Parameter                       |  | Placebo       | DTX401                | Placebo<br>→DTX401 |
|---------------------------------|--|---------------|-----------------------|--------------------|
| Week 48                         |  |               |                       |                    |
| n                               |  | 23            | 18                    | 17                 |
| Mean (SD)                       |  | 3.52 (2.64)   | 3.23 (1.58)           | 3.64<br>(1.50)     |
| Change from baseline, mean (SD) |  | 0.79 (2.55)   | 1.14 (1.62)           | 0.39<br>(2.64)     |
| LS mean difference (95% CI)     |  |               | 0.06 (-1.19,<br>1.32) |                    |
| p-value                         |  |               | 0.919                 |                    |
| Week 96                         |  |               |                       |                    |
| n                               |  | -             | 13                    | -                  |
| Mean (SD)                       |  | -             | 3.52 (1.61)           | -                  |
| Change from baseline, mean (SD) |  | -             | 1.51 (1.90)           | -                  |
| Plasma uric acid (mg/dL)        |  |               |                       |                    |
| Baseline                        |  |               |                       |                    |
| n                               |  | 24            | 20                    | 19                 |
| Mean (SD)                       |  | 6.64 (1.63)   | 6.30 (1.56)           | 6.28<br>(1.48)     |
| Week 48                         |  |               |                       |                    |
| n                               |  | 23            | 19                    | 17                 |
| Mean (SD)                       |  | 6.32 (1.23)   | 6.95 (2.09)           | 7.01<br>(1.68)     |
| Change from baseline, mean (SD) |  | -0.22 (1.57)  | 0.62 (1.42)           | 0.58<br>(1.17)     |
| Week 96                         |  |               |                       |                    |
| n                               |  | -             | 14                    | -                  |
| Mean (SD)                       |  | -             | 7.45 (2.17)           | -                  |
| Change from baseline, mean (SD) |  | -             | 0.85 (2.57)           | -                  |
| Triglycerides (mg/dL)           |  |               |                       |                    |
| Baseline                        |  |               |                       |                    |
| n                               |  | 25            | 21                    | 19                 |
| Mean (SD)                       |  | 335.5 (182.5) | 337.2 (198.3)         | 335.5<br>(175.3)   |
| Week 48                         |  |               |                       |                    |
| n                               |  | 23            | 20                    | 17                 |
| Mean (SD)                       |  | 354.0 (164.9) | 546.2 (493.6)         | 580.8<br>(348.5)   |
| Change from baseline, mean (SD) |  | 7.4 (179.8)   | 209.8 (383.1)         | 231.0<br>(346.2)   |
| Week 96                         |  |               |                       |                    |
| n                               |  | -             | 15                    | -                  |
| Mean (SD)                       |  | -             | 579.3 (372.9)         | -                  |
| Change from baseline, mean (SD) |  | -             | 245.3 (322.6)         | -                  |

Source: Clinical Reviewer

Abbreviations: CFC, controlled fasting challenge; PEAP, Primary Efficacy Assessment Period; SD, standard deviation

Crossover period analyses were not prespecified for efficacy analyses and carried limitations for efficacy interpretation. Once the double-blind period ends, patients are no longer randomly assigned to treatment groups, meaning the two groups may differ in ways that could influence results. Analyses restricted to patients who completed the crossover phase may also not fully represent the overall study population. Additionally, blinding was functionally compromised during the crossover period, as patients would

have been aware of whether they received treatment earlier (at study start) or later (after Week 48), making it difficult to rule out the influence of patient expectations on reported outcomes.

Given these limitations, the FDA clinical team reviewed the crossover results as descriptive only; no p-values are reported, and these data are not presented as formal efficacy evidence in this review. That said, the crossover findings are directionally consistent with the double-blind period results. Among the 15 of 21 GENGLYCOS-treated patients with available data at Week 96, the mean (SD) percent change from baseline in daily cornstarch intake was -60.8% (19.7%), and the mean (SD) change in the number of daily cornstarch doses was -1.9 (1.5). Among the 19 of 21 patients with available glucose data at Week 96, the mean (SD) change from baseline in the percentage of glucose values in the hypoglycemic range (<70 mg/dL) was +5.2% (6.3%).

### **FDA Summary of Efficacy for Phase 3 Study DTX401-CL301**

DTX401 demonstrated a statistically significant reduction in daily cornstarch intake, with treated patients achieving a 41% reduction from baseline compared to 10% in the placebo group (LS mean difference: ~-31 percentage points; 95% CI: -40.8%, -20.9%;  $p < 0.0001$ ), along with a reduction in daily dosing frequency of approximately one dose per day ( $p = 0.0004$ ).

CGM data showed a directionally favorable shift in glucose distribution. Hyperglycemia (>120 mg/dL) was reduced by 9.2% relative to placebo, and time in the optimal range (70–120 mg/dL) was better preserved in the DTX401 group (-0.51% vs. -6.54% in placebo; difference: +6.03%), though neither reached statistical significance. A modest increase in hypoglycemic exposure (<70 mg/dL) was observed in the DTX401 group and warrants continued monitoring.

TTH during the CFC improved by 0.5 and 1.1 hours in the placebo and DTX401 groups, respectively; the between-group difference of 0.6 hours was small and not statistically significant (95% CI: -1.7, 2.9;  $p = 0.590$ ).

Metabolic parameters did not show expected improvements alongside reduced cornstarch intake, as DTX401-treated patients trended toward greater elevations in triglycerides relative to placebo.

Crossover efficacy findings, based on observed data, were directionally consistent with those from the double-blind period.

#### **8.1.1.6.9 Data Quality and Integrity**

##### Data/Applicant's Position:

There are no issues regarding data quality and submission integrity. Not applicable.

##### The FDA's Assessment:

FDA concurs.

### **8.1.1.6.10 Efficacy Results – Secondary and Other Relevant Endpoints**

#### **8.1.1.6.10.1 Total Daily Cornstarch Doses (Key Secondary Endpoint)**

Data:

*PEAP:* At Week 48, statistically significant reductions in the number of total daily cornstarch doses were observed with DTX401 treatment compared with Placebo, with an LS mean (SE) change from Baseline in total daily cornstarch doses of -0.2 (0.2) in the Placebo group and -1.1 (0.2) in the DTX401 group ( $p = 0.0011$ ) (DTX401-CL301 Week 96 CSR Table 14.2.1.2.1.1).

*Crossover Period:* At 48 weeks after treatment with DTX401 (ie, Week 96), subjects in the Crossover Placebo→DTX401 group showed a mean (SD) change from Crossover Baseline in total daily cornstarch doses of -1.6 (1.9), greater in magnitude than that observed in Placebo and DTX401 groups within the same timeframe post-dose in the PEAP. Furthermore, the number of daily cornstarch doses continued to decline in the DTX401 group on longer follow-up after the PEAP. At Week 96, the mean (SD) change from Baseline in total daily cornstarch doses was -1.9 (1.5) in the DTX401 group (DTX401-CL301 Week 96 CSR Table 14.2.1.2.1.2).

*Follow-up Period:* At the last available visit for all subjects, the mean (SD) change from Crossover Baseline in number of total daily doses of cornstarch was -1.8 (1.5) in the Crossover Placebo→DTX401 group and the mean (SD) change from Baseline in number of total daily doses of cornstarch was -2.0 (1.4) in the DTX401 group (DTX401-CL301 Week 96 CSR Table 14.2.1.2.1.2).

#### ***Additional/Supplementary Analysis***

*Nighttime cornstarch doses:* At Week 48, there was an increase in the number of nighttime cornstarch doses in the Placebo group vs a decrease in the DTX401 group. The LS mean (SE) change from Baseline to Week 48 in the number of nighttime cornstarch doses was +0.7 (0.3) vs -0.2 (0.3) in the Placebo ( $n = 14$ ) and DTX401 groups ( $n = 14$ ), respectively (LS mean difference [SE]: -0.9 [0.4],  $p = 0.0105$ ) (DTX401-CL301 Week 96 CSR Table 14.2.1.2.2.2.1). At 48 weeks after treatment with DTX401 (ie, Week 96), for the Crossover Placebo→DTX401 group ( $n = 12$ ), nighttime cornstarch doses were markedly reduced from Crossover Baseline (mean [SD] change from Baseline of -1.1 [1.7] doses). At Week 96 in the DTX401 group ( $n = 12$ ), a further decline in nighttime cornstarch doses was observed in the DTX401 group (mean [SD] change from Baseline of -0.8 [0.7] doses). At Week 96, two-thirds of subjects treated with DTX401 eliminated at least one nighttime cornstarch dose (DTX401-CL301 Week 96 CSR Tables 14.2.1.2.2.2.2, 14.2.1.2.2.2.4).

Applicant's Position:

Total daily cornstarch dose frequency, including nighttime cornstarch doses, showed similar patterns of statistically significant reductions with DTX401 vs Placebo as the

primary endpoint of total daily cornstarch intake, with greater reductions observed during the Crossover Period.

#### 8.1.1.6.10.2 Endpoints Related to Glycemic Control

##### Glycemic Control Assessed by CGM

###### Data:

Change from Baseline in percentage of glucose values in severe hypoglycemic (< 54 mg/dL), hypoglycemic (< 70 mg/dL; key secondary endpoint), and euglycemic range (70-120 mg/dL; secondary endpoint) assessed by CGM is presented in [Table](#). Additionally, nighttime glycemic control, assessed by rate of decline of nighttime glucose values on CGM data collected from 12 am to 6 am is included.

**Table 26: Applicant – Glycemic Control: Secondary Endpoints and Additional Analyses (mITT Analysis Set)**

| Assessment Analysis                                                           | Placebo (N = 24)                                | DTX401 (N = 20) | Crossover Placebo →DTX401 (N = 19) <sup>a, b</sup> |
|-------------------------------------------------------------------------------|-------------------------------------------------|-----------------|----------------------------------------------------|
| Percentage of Glucose Values in Hypoglycemic Range by CGM (< 70 mg/dL)        |                                                 |                 |                                                    |
| Change from Baseline to Week 48, LS Mean (SE)                                 | +0.08 (0.86)                                    | +3.13 (0.96)    | +2.44 (3.36) <sup>b</sup>                          |
|                                                                               | Week 48 p-value <sup>c</sup> : < 0.0001 (NI)    |                 |                                                    |
| Change from Baseline to Week 96, Mean (SD)                                    | NA                                              | +5.20 (6.32)    | -0.45 (0.64) <sup>d</sup>                          |
| Percentage of Glucose Values in Severe Hypoglycemic Range by CGM (< 54 mg/dL) |                                                 |                 |                                                    |
| Change from Baseline to Week 48, LS Mean (SE)                                 | +0.23 (0.23)                                    | +0.74 (0.26)    | +0.38 (0.69) <sup>b</sup>                          |
|                                                                               | Week 48 p-value <sup>c, e</sup> : < 0.0001 (NI) |                 |                                                    |
| Change from Baseline to Week 96, Mean (SD)                                    | NA                                              | +1.24 (1.42)    | -0.65 (0.78) <sup>d</sup>                          |
| Percentage of Glucose Values in the 70 to 120 mg/dL Range by CGM              |                                                 |                 |                                                    |
| Change from Baseline to Week 48, LS Mean (SE)                                 | -6.54 (2.64)                                    | -0.51 (2.93)    | +11.47 (15.88) <sup>b</sup>                        |
|                                                                               | Week 48 p-value <sup>c, e</sup> : < 0.0001 (NI) |                 |                                                    |
| Change from Baseline to Week 96, Mean (SD)                                    | NA                                              | +8.87 (14.73)   | +11.35 (22.70) <sup>d</sup>                        |
| Rate of Decline of Nighttime Glucose Values (mg/dL/hr)                        |                                                 |                 |                                                    |
| Change from Baseline to Week 48, LS Mean (SE)                                 | +0.96 (1.52)                                    | -0.48 (1.69)    | -2.36 (6.80) <sup>d</sup>                          |

| <b>Assessment Analysis</b>                 | <b>Placebo (N = 24)</b>                 | <b>DTX401 (N = 20)</b> | <b>Crossover Placebo →DTX401 (N = 19)<sup>a, b</sup></b> |
|--------------------------------------------|-----------------------------------------|------------------------|----------------------------------------------------------|
|                                            | Week 48 p-value <sup>c, e</sup> = 0.516 |                        |                                                          |
| Change from Baseline to Week 96, Mean (SD) | NA                                      | -2.81 (8.09)           | +0.81 (3.22) <sup>d</sup>                                |

<sup>a</sup> This column includes results for subjects who were in the Placebo group at Day 1 who crossed over and received DTX401 treatment at Week 48. Baseline for the Crossover Placebo→DTX401 group is the last observation prior to DTX401 dosing at Week 48.

<sup>b</sup> Data for the Crossover Placebo→DTX401 group are reported as mean (SD).

<sup>c</sup> The Week 48 p-value is for the null hypothesis of no difference in mean percent change (or change) from Baseline to Week 48 between the DTX401 and placebo groups at Week 48 from a mixed-model for repeated measures. No p-values were calculated at Week 96.

<sup>d</sup> Results are shown for the 2 subjects in the Crossover Placebo→DTX401 group who reached the Week 96 timepoint as of the data cut off; since the n is small this should be factored into interpretation of results.

<sup>e</sup> The p-value is nominal for descriptive purpose only.

CGM, continuous glucose monitoring; LS, least squares; MMRM, mixed model repeated measures; NA, not applicable; NI, non-inferiority

Source: DTX401-CL301 Week 96 CSR Tables 14.2.1.3.1.1, 14.2.1.3.1.2, 14.2.1.3.2.1.2, 14.2.1.3.2.1.4, 14.2.1.7.1.1, 14.2.1.7.1.2, 14.2.1.20.1.1, 14.2.1.20.1.2

### **Additional CGM Analyses**

In addition to evaluating all CGM data in subjects, data from subjects with ≥ 70% of CGM data available over 14 consecutive days was evaluated. When this threshold was applied, the difference observed between the Placebo and DTX401 groups was reduced compared with “all CGM data” in the primary analysis (DTX401-CL301 Week 96 CSR Table 14.2.1.3.3.3).

### **Glycemic Control assessed by Fasting Tolerance in a Controlled Fasting Challenge**

#### Data:

Change from Baseline in time to hypoglycemia (< 54 mg/dL; secondary endpoint), and normalized time to hypoglycemia is presented in Table. As cornstarch was expected to reduce following treatment with DTX401, the time to hypoglycemia in minutes was normalized by the amount of cornstarch in grams taken to start the controlled fasting challenge to compare DTX401 and Placebo groups.

At Baseline, the mean (SD) time to hypoglycemia (TTH) during the CFC was 6.18 (3.07) hours in the Placebo group and 7.10 (4.09) hours in the DTX401 group (DTX401-CL301 Week 96 CSR Table 14.2.1.6.1.1). At Baseline, the mean (SD) TTH in a CFC normalized by the amount of cornstarch used prior to fasting was comparable in both groups: 10.30 (8.96) min/g in the Placebo group and 10.36 (7.48) min/g in the DTX401 group (DTX401-CL301 Week 96 CSR Table 14.2.1.6.2.1).

**Table 27: Applicant – Time to Hypoglycemia and Normalized Time to Hypoglycemia (mITT Analysis Set)**

Analysis Set/

| Assessment Analysis                            | Placebo (N = 24)                      | DTX401 (N = 20) | Crossover Placebo →DTX401 (N = 19) <sup>a, b</sup> |
|------------------------------------------------|---------------------------------------|-----------------|----------------------------------------------------|
| Time to Hypoglycemia (TTH) during a CFC, hours |                                       |                 |                                                    |
| Change from Baseline to Week 48, LS Mean (SE)  | +0.50 (0.80)                          | +1.12 (0.91)    | +1.34 (3.44)                                       |
|                                                | Week 48 p-value <sup>c</sup> = 0.590  |                 |                                                    |
| Change from Baseline to Week 96, Mean (SD)     | NA                                    | +1.13 (3.69)    | NA                                                 |
| Normalized TTH during a CFC, minutes per gram  |                                       |                 |                                                    |
| Change from Baseline to Week 48, LS Mean (SE)  | + 2.42 (3.04)                         | + 12.34 (3.50)  | + 25.79 (45.19)                                    |
|                                                | Week 48 p-value <sup>c</sup> = 0.0269 |                 |                                                    |
| Change from Baseline to Week 96, Mean (SD)     | NA                                    | + 19.29 (28.38) | NA                                                 |

<sup>a</sup> This column includes results for subjects who were in the Placebo group at Day 1 who crossed over and received DTX401 treatment at Week 48. Baseline for the Crossover Placebo→DTX401 group is the last observation prior to DTX401 dosing at Week 48.

<sup>b</sup> Data for the Crossover Placebo→DTX401 group are reported as mean (SD).

In Study DTX401-CL301, normalized TTH was calculated as time to hypoglycemia (minutes) divided by pre-fasting cornstarch (g) and it was calculated only in cases where subjects started their CFC with cornstarch (i.e. subjects who were not on an evening dose of cornstarch and started their CFC from an evening meal were not included to avoid skewing of data).

CFC, controlled fasting challenge; TTH, time to hypoglycemia.

<sup>c</sup> The p-value is nominal for descriptive purpose only.

Source: DTX401-CL301 Week 96 CSR Table 14.2.1.6.1.1, Table 14.2.1.6.1.2, Table 14.2.1.6.2.1, Table 14.2.1.6.2.2

#### Applicant's Position:

***Appropriateness of cornstarch reductions following DTX401 treatment was evidenced across multiple secondary endpoints by maintained low levels of hypoglycemia and improvements in glucose values in normal range, nighttime glycemic control and fasting tolerance.***

The totality of data available in the study indicates that reductions in cornstarch did not come at the expense of glycemic control. Following nutritional optimization and stabilization in the Screening Period, maintenance of glycemic control was evident across multiple concordant endpoints with significant cornstarch reductions during the PEAP. In fact, improved euglycemia and fasting tolerance were observed in the context

of even greater reductions in cornstarch achieved during the Crossover Period for both the Crossover Placebo→DTX401 group and the DTX401 group.

A higher percentage of glucose values <70 mg/dL were observed following DTX401 compared to Placebo during the PEAP, however; this was deemed to not be clinically meaningful based on the following:

- Pre-defined statistical non-inferiority was met in the PEAP comparing the change from Baseline in the percentage of glucose values in hypoglycemia <70 mg/dL and euglycemic range (70-120 mg/dL) as assessed by CGM. Superiority of DTX401 over Placebo was not demonstrated.
- In the Crossover Placebo→DTX401 group, the increase from Baseline in percentage of values <70 mg/dL was smaller than the PEAP even with substantially greater reductions in cornstarch, Improvements in euglycemic range in the Crossover Placebo→DTX401 group likely reflect improved management of subjects, less hyperglycemia and less change in hypoglycemia from Baseline. Improved trends in nighttime glucose control were also observed in the Crossover Period.
- DTX401 retains the native *G6PC* promoter and enhancer elements, and upregulation and expression of G6Pase is expected to occur when glucose values fall < 70 mg/dL consistent with normal glucose physiology. Evaluation of severe hypoglycemia (< 54 mg/dL) is considered equally, if not more important, to observe and monitor clinically.
- No correlation between cornstarch reduction and percentage of values < 70 mg/dL in the DTX401 group during the PEAP (Pearson correlation coefficient = -0.26 overall and -0.05 for DTX401 group).
- Reductions in cornstarch resulted in improvements in fasting tolerance and protection from severe hypoglycemia (<54mg/dL) assessed in the CFC, with 5-fold larger improvement in the DTX401 group during the PEAP and further improvements observed in the Crossover Period for both treatment groups.

The FDA's Assessment:

Refer to The FDA's Assessment for Efficacy in Section [8.1.1.6.8](#).

#### **8.1.1.6.11 Dose/Dose Response**

Data/Applicant's Position:

Not applicable. Dose-response analyses were not conducted in the Phase 3 study as only a single dose level ( $1 \times 10^{13}$  GC/kg) was evaluated. Please refer to Section [6.3.2.2](#) for dose-response analysis.

The FDA's Assessment:

FDA concurs.

#### 8.1.1.6.12 Durability of Response

Data:

Refer to Section [8.1.4.3](#).

The FDA's Assessment:

Refer to The FDA's Assessment for Efficacy in Section [8.1.1.6.8](#).

#### 8.1.1.6.13 Persistence of Effect

Data:

Refer to Section [8.1.4.3](#).

The FDA's Assessment:

Refer to The FDA's Assessment for Efficacy in Section [8.1.1.6.8](#).

#### 8.1.1.6.14 Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Data:

##### PGIC (key secondary endpoint)

*PEAP:* No statistically significant difference was observed for PGIC 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,  $p = 0.131$ ). At Week 48, the median PGIC score was 1.0 (minimally improved) for the Placebo group ( $n = 23$ ) and 2.0 (moderately improved) for the DTX401 group ( $n = 19$ ). At Week 48, 52% ( $n = 12/23$ ) of Placebo group subjects reported improved GSDIa on the PGIC vs 79% ( $n = 15/19$ ) of DTX401 group subjects (DTX401-CL301 Week 96 CSR Table 14.2.1.4.1.1).

*Crossover Period:* At 48 weeks after DTX401 treatment (ie, Week 96), the mean (SD) PGIC score was 2.1 (1.0) (median was 2.0) for the Crossover Placebo→DTX401 group ( $n = 19$ ), and 95% of subjects ( $n = 18/19$ ) in the Crossover Placebo→DTX401 group reported improved GSDIa on the PGIC at Week 96. For the DTX401 group ( $n = 12$ ) at Week 96, the mean (SD) PGIC score was 1.4 (1.2) (median = 1.0), and 83% of DTX401 group subjects ( $n = 10/12$ ) reported improved GSDIa on the PGIC at Week 96 (DTX401-CL301 Week 96 CSR Table 14.2.1.4.1.2).

Among Crossover Placebo→DTX401 group subjects with available data reporting any level of improvement on PGIC at Week 96 (48 weeks post-DTX401) ( $n = 17/19$ ), average reduction in cornstarch intake was 64%. Among DTX401 group subjects reporting any level of improvement on PGIC at Week 96 ( $n = 9/12$ ), average reduction in cornstarch intake was 61% (DTX401-CL301 Week 96 CSR Table 14.2.1.4.3.3).

*Follow-up Period:* At the last available visit for all subjects, the mean (SD) PGIC score for the Crossover Placebo→DTX401 group was 2.1 (0.9) (median = 2.0), and 95% of these subjects ( $n = 18/19$ ) reported improved GSDIa on the PGIC at this timepoint. The mean (SD) PGIC score for the DTX401 group was 1.6 (1.5) (median = 2.0), and 84% ( $n$

= 16/19) reported improved GSDIa on the PGIC at this timepoint (DTX401-CL301 Week 96 CSR Table 14.2.1.4.1.2).

### **Patient Experience Interviews**

Results of trial interviews conducted in Study DTX401-CL301 are summarized in Section 10.4.6 of the DTX401-CL301 Week 96 CSR.

#### The Applicant's Position:

#### ***Improvements in GSDIa disease experience were observed after treatment with DTX401***

A high proportion of subjects reported improved GSDIa on the PGIC following DTX401 treatment at Week 48 with a greater proportion of subjects reporting improved GSDIa across both treatment groups at Week 96, which was sustained at the last available visit. During trial patient experience interviews, DTX401-treated subjects most frequently reported reductions in cornstarch intake, less hypoglycemia, less tiredness, and improvements in physical function, social, and diet/daily regimen impacts, which were all identified as most important to treat during DTX401-CL301 Baseline interviews.

#### The FDA's Assessment:

Refer to The FDA's Assessment for Efficacy in Section [8.1.1.6.8](#).

### **8.1.1.6.15 Additional Analyses Conducted on the Individual Trial**

#### **Diet**

##### Data:

As cornstarch intake was reduced following treatment with DTX401, subjects transitioned from a GSDIa high carbohydrate, cornstarch-dependent diet (60 –70% of calories per international GSDIa nutritional guidance), to a food-based diet with an improved macronutrient distribution. At Baseline, a high percentage of calories from carbohydrates (cornstarch and non-cornstarch diet) of 62.4 (9.6) % for the Placebo group and 66.5 (6.7) % for the DTX401 group was reported, consistent with recommended dietary carbohydrate intake in patients with GSDIa. At Week 48 in the Placebo group (n = 23), the mean (SD) percentage of calories from carbohydrate (cornstarch and diet) was 60.3 (11.1) % and remained consistent with Baseline. At Week 48 in the DTX401 group (n = 19), the mean (SD) percentage of calories from carbohydrate (cornstarch and diet) was 56.4 (10.8) % and at Week 96 (n = 13) was 51.6 (9.6) %. At 48 weeks after treatment with DTX401, in the Crossover Placebo→DTX401 group (n = 16) the mean (SD) percentage of total calories from carbohydrate (cornstarch and diet) was 46.1 (9.7) % (DTX401-CL301 Week 96 CSR Tables 14.2.3.4.3, 14.2.3.4.4).

##### Applicant's Position:

Following DTX401 treatment, there was an evident shift from a cornstarch-dependent diet towards a more nutritionally balanced, non-cornstarch dependent diet, with a

macronutrient distribution consistent with the US Dietary Guidelines for the general population (USDA and USDHHS, 2020).

#### The FDA's Assessment:

FDA did not conduct a diet assessment, as this was not a prespecified efficacy endpoint in the study protocol.

### **8.1.2 Studies 401GSDIA01 and 401GSDIA02 (Supportive Studies)**

#### **8.1.2.1 Trial Design**

Study 401GSDIA01 was a Phase 1/2 open-label, single-arm, multicenter safety and dose-finding study in adult subjects ( $\geq 18$  years of age) with GSDIa. Twelve eligible subjects were enrolled sequentially into 4 cohorts of 3 subjects each and received a single IV infusion of DTX401 (Cohort 1:  $2.0 \times 10^{12}$  GC/kg; Cohorts 2-4:  $6.0 \times 10^{12}$  GC/kg per qPCR), with corticosteroids (prednisone) to manage ALT elevation. Subjects were monitored for 52 weeks after administration of DTX401.

Study 401GSDIA02 was a long-term follow-up study to evaluate the safety and efficacy of DTX401 in subjects who completed Study 401GSDIA01. No IP was administered in this study.

#### **8.1.2.2 Study Results**

A brief summary of key efficacy results are included below, with detailed results available in the respective study reports included in the dossier.

- **Cornstarch Intake and Dosing:** At Week 52, the mean (SD) percent reduction from Baseline in daily cornstarch intake ( $n = 10$ ) was 68 (19.5) % ( $p$ -value  $< 0.0001$ ). The mean (SD) reduction from Baseline in nighttime cornstarch intake in subjects taking nighttime cornstarch at Baseline across Cohorts ( $n = 4$ ) was 87 (26.5) % (401GSDIA02 CSR Table 14.2.1.4, Figure 16.2.6.1.5.2).

At the last available visit in Study 401GSDIA02 (ie, after a mean [SD] duration of follow-up of 254 [45] weeks), the mean (SD) percent reduction from Baseline in daily cornstarch intake for individual subjects ( $n = 12$ ) was 74 (22.6) %. The number of daily doses was reduced by at least half from Baseline for 6 out of 12 subjects and amounted to 2 or fewer daily doses. Moreover, among the 5 subjects who were taking nighttime cornstarch at Baseline, 3 subjects (60%) were able to discontinue nighttime cornstarch (401GSDIA02 CSR Table 14.2.1.4, Figures 16.2.6.1.6.2, 16.2.6.1.7.4).

- **Glycemic Control by CGM:** Limited CGM data were available for Cohorts 3 and 4 only. In general low levels of hypoglycemia were maintained on long-term follow-up post-DTX401 (401GSDIA02 CSR Table 14.2.1.6.2) and key results are summarized in [Table](#).
- **Fasting Tolerance in CFCs:** The mean (SD) TTH normalized by amount of cornstarch pre-CFC was 18.25 (13.52) mins/g at Baseline, and the mean (SD) change from Baseline was 1.48 (20.40) mins/g at Week 52, increased to 103.64

(73.56) mins/g by Week 104, and increased to 132.41 (265.72) mins/g at the last available visit (401GSDIA02 CSR Table 14.2.1.2.1).

- **PGIC:** At Week 52, the median PGIC score was 3.0 (much improved), 89% of subjects (n = 8/9) in Cohorts 2-4 reported improvement, 11% (n = 1/9) reported no change, and no subject reported worsening GSDIa on the PGIC. At the last available visit, the median PGIC score was 2.5, 75% of subjects (n = 9/12) reported improvement, 17% (n = 2/12) reported no change, and 8% (n = 1/12) reported worsening GSDIa on the PGIC (401GSDIA02 CSR Table 14.2.1.12.1, 14.2.1.12).
- **Diet:** The percentage of total calories from carbohydrate (cornstarch and non-cornstarch diet) decreased from 61% at Baseline to 43% at Week 52 and 44% at the last available visit. The percentage of calories from cornstarch intake decreased from 47% at Baseline, to 18% at Week 52 and 13% at the last available visit (401GSDIA02 CSR Table 14.2.1.5.2).

#### Applicant's Position

Studies 401GSDIA01 and 401GSDIA02 provide supportive evidence of DTX401 efficacy in patients with GSDIa, including reduction in cornstarch intake and dosing with maintained glycemic control and improved fasting tolerance and patient experience. These findings are highly consistent with the results of the Crossover Period of the Phase 3 study and results were sustained over long-term follow-up.

#### The FDA's Assessment of Efficacy and Safety:

Title: Phase 1/2 open-label, single-arm, multicenter, dose-finding study evaluating the safety, tolerability, and efficacy of a single intravenous (IV) dose of DTX401 in adults with GSDIa.

ClinicalTrials.gov: NCT03517085

This is the first in human study conducted at 6 centers in the U.S. (4), Canada (1), Netherlands (1), and Spain (1).

#### **Objectives**

Safety, preliminary efficacy and dose finding.

This study employed an adaptive design for dose escalation. No control group was included, and no nutritional optimization period was required prior to enrollment. All subjects received a single peripheral intravenous (IV) infusion of DTX401 and were followed for 52 weeks post-dose.

Subjects were enrolled into one of four dose cohorts below, each receiving a single IV dose of DTX401 accompanied by either a reactive or prophylactic corticosteroid regimen to manage anticipated hepatic immune responses.

- Cohort 1 (n=3):  $2.0 \times 10^{12}$  GC/kg; reactive steroid course (40 mg/day, 6 weeks) initiated after ALT elevation (Reactive)
- Cohort 2 (n=3):  $6.0 \times 10^{12}$  GC/kg; reactive steroid course (40 mg/day, 6 weeks) initiated after ALT elevation (Reactive)
- Cohort 3 (n=3):  $6.0 \times 10^{12}$  GC/kg; reactive steroid course (60 mg/day, 7 weeks) initiated after ALT elevation (Optimized Reactive)
- Cohort 4 (n=3):  $6.0 \times 10^{12}$  GC/kg; prophylactic steroid course (60 mg/day, 8 weeks) initiated on Day 1

FDA CMC team confirmed that the dose level of  $6.0 \times 10^{12}$  GC/kg used in the Phase 1/2 study, as measured by qPCR, is analytically equivalent to  $1.0 \times 10^{13}$  GC/kg as measured by Droplet Digital PCR (ddPCR) in the Phase 3 study.

### Inclusion Criteria

- Males and females  $\geq 18$  years of age
- Documented GSDIa confirmed by molecular testing
- Documented history of  $\geq 1$  hypoglycemic event with glucose  $< 60$  mg/dL ( $< 3.33$  mmol/L)
- GSDIa disease stable, evidenced by no hospitalization for severe hypoglycemia during the 4-week period preceding the Screening Visit

### Exclusion Criteria

- Screening or Baseline (Day 0) glucose level  $< 60$  mg/dL ( $< 3.33$  mmol/L)
- Prior liver transplant, including hepatocyte cell therapy/transplant
- Liver adenoma  $> 5$  cm, or  $> 3$  cm with documented annual growth rate  $\geq 0.5$  cm/year
- Significant hepatic inflammation or cirrhosis, evidenced by imaging or laboratory abnormalities (ALT or AST  $> \text{ULN}$ , total bilirubin  $> 1.5 \times \text{ULN}$ , or alkaline phosphatase  $> 2.5 \times \text{ULN}$ )
- Serum creatinine  $> 2.0$  mg/dL
- Triglycerides  $\geq 1000$  mg/dL at Screening
- Anti-AAV8 neutralizing antibody titer  $\geq 1:5$

### Efficacy Results

The Phase 1/2 study protocol underwent six amendments, several of which introduced changes with implications for the interpretation of efficacy results. This is of particular concern given the single-arm design and the lack of a concurrent control group.

- The change from Baseline in time (in minutes) to first hypoglycemic event (defined as glucose  $\leq 60$  mg/dL, and later changed to  $\leq 54$  mg/dL) during a CFC at 12, 24, and 52 weeks after IV administration of DTX401.

The change from baseline in TTH during a CFC, defined initially as glucose  $\leq 60$  mg/dL and later revised to  $\leq 54$  mg/dL via Protocol Amendment 6 (16 February 2021).

Overall, the mean TTH increased from 3.4 hours at baseline to 5.9 hours at Week 12, and 5.2 hours at both Week 24 and Week 52. Among the 9 patients who received the high dose ( $6.0 \times 10^{12}$  GC/kg), results varied substantially by cohort and steroid regimen, as shown in [Table 28](#) below.

**Table 28: FDA – TTH in CFC (N=12)**

| Cohort                                               | Mean Change From Baseline to Week 52       | Individual Range   |
|------------------------------------------------------|--------------------------------------------|--------------------|
| Cohort 2 (Patients 4–6; reactive steroids)           | –1.8 (SD 1.7) hours                        | –3.3 to +0.1 hours |
| Cohort 3 (Patients 7–9; optimized reactive steroids) | –0.6 (SD 0.1) hours (2 patients with data) | –0.6 to –0.6 hours |
| Cohort 4 (Patients 10–12; prophylactic steroids)     | +3.6 (SD 2.7) hours                        | +1.5 to +6.6 hours |

Source: Clinical review team

Abbreviations: CFC, controlled fasting challenge; SD, standard deviation; TTH, time to hypoglycemia

- Notable cohort-specific observations:
  - Cohort 2: TTH decreased and all 3 patients had high insulin or low cortisol at Week 52.
  - Cohort 3: Data at Week 52 is available for only 2 patients. All patients in this cohort had low cortisol levels throughout the challenges.
  - Cohort 4: All 3 patients showed increases in time to hypoglycemia, with the best outcomes among the high-dose cohorts.

These results are difficult to interpret. The fasting challenge protocol underwent substantial modifications across cohorts and over time including changes to the pre-CFC cornstarch dose (from 35 g to 5 g to individualized dosing), the pre-CFC dinner carbohydrate content, and the hypoglycemia stopping threshold (from 60 mg/dL to 54 mg/dL). While these modifications were scientifically motivated, they introduced considerable variability that limits the comparability of results across cohorts and timepoints. The evolving study design, combined with the significant confounding variables inherent to a single-arm, open-label adaptive trial design, introduces substantial bias and uncertainty that precludes a definitive determination of whether the observed effects reflect a true treatment response.

- Reduction in CS use (N=12)

All 12 subjects had a reduction in prescribed daily cornstarch intake by Week 52, with a mean reduction of 70% (SD 23%) and individual reductions ranging from 28% to 100%. Six subjects had their prescribed cornstarch frequency reduced by half or more, and no subject had an increase from baseline in prescribed frequency.

However, the magnitude of cornstarch reduction, while notable, warrants cautious interpretation. Dose adjustments were governed by investigator discretion rather than pre-specified criteria, and intake was assessed through

averaged 3-day paper diaries. These methodological limitations introduce imprecision and undermine the reliability of cornstarch intake as a quantitative efficacy measure.

- Continuous Glucose Monitoring (N=6)  
CGM (Dexcom) was only implemented starting from Protocol Amendment 4 (Amendment 5 globally, dated October 2019) and was therefore only available for Cohorts 3 and 4 from baseline onward. The data were available from 6 patients.
  - Cohort 3: Average monthly time in normoglycemia (60–120 mg/dL) increased from 72% at baseline to 86% at end of study (Weeks 49–52), despite a 60% reduction in average daily cornstarch intake (288 g to 115 g).
  - Cohort 4: Average monthly time in normoglycemia remained stable at approximately 74–75% despite a 52% reduction in cornstarch intake (273 g to 132 g).

CGM data provide supportive but non-definitive evidence of glycemic improvement, given the unblinded nature of the monitoring and the limited cohort coverage (only 2 of 4 cohorts).

- Metabolic Laboratory Parameters (N=12)

The following [Table 29](#) showed mean changes from baseline to Week 52 were observed across all 12 patients.

**Table 29: FDA – Metabolic Laboratory Parameters (N=12)**

| Parameter                    | Mean Change From Baseline to Week 52 (SD) | Direction             |
|------------------------------|-------------------------------------------|-----------------------|
| Total cholesterol            | +66 mg/dL (58)                            | ↑ Increase            |
| LDL-C                        | +23 mg/dL (22)                            | ↑ Increase            |
| Triglycerides                | +287 mg/dL (254)                          | ↑ Increase            |
| Uric acid                    | +1.0 mg/dL (2.1)                          | ↑ Modest increase     |
| Lactate (fasting challenge)* | Not summarized as change from baseline    | ↑ During hypoglycemia |

Source: Clinical review team

\*Lactate was measured at the start and end of each controlled fasting challenge rather than as a change from baseline to Week 52. Across all cohorts, lactate rose as glucose fell, frequently exceeding 4 mmol/L at hypoglycemia, suggesting that hepatic gluconeogenesis under physiologic stress had not fully normalized following DTX401 treatment.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; SD, standard deviation

Cornstarch reduction following DTX401 administration did not result in metabolic improvement at Week 52; rather, metabolic parameters worsened, with hypertriglyceridemia showing the most substantial increase. The wide standard deviations reflect considerable inter-patient variability in treatment response.

- PGIC (n=9) who received the dose of  $6.0 \times 10^{12}$  GC/kg
  - 5 of 9 (56%) reported GSD Ia was "much improved"
  - 1 of 9 (11%) reported "moderately improved"
  - 2 of 9 (22%) reported "minimally improved"
  - 1 of 9 (11%) reported "no change"
  - No patient reported worsening

This patient-reported outcome is highly susceptible to bias given the single-arm design and subjectivity of the measure.

## Safety Results

All 12 subjects experienced at least one TEAE and at least one TEAE. no subject experienced a dose-limiting toxicity, study discontinuation, or death due to a TEAE. All TEAEs were Grade 1 or 2.

Five SAEs were reported in 4 subjects (33%), including lactic acidosis and nephrolithiasis (same patients), metabolic/glycemic instability, cellulitis, and migraine. All resolved and were assessed as unrelated to study drug, attributed to underlying GSD Ia or pre-existing conditions.

**Most Common TEAEs:** The most frequently reported TEAEs were headache (67%), ALT elevation (50%), and diarrhea or vomiting (42% each), consistent with the known AAV gene therapy safety profile and prednisone-related gastrointestinal effects.

### *Liver Enzyme Elevations*

All 12 subjects experienced at least one TEAE associated with elevated liver enzymes. ALT peaked between Weeks 6–12, consistent with T-cell-mediated immune responses to AAV capsid proteins. Peak ALT values were lower in Cohort 4 (157 U/L) versus Cohort 3 (323 U/L), suggesting prophylactic steroids may attenuate peak elevations. All transaminase elevations were Grade 1 or 2, asymptomatic, and resolved with corticosteroid treatment.

### *HPA Axis Suppression*

A notable safety consideration is HPA axis suppression associated with prolonged prednisone use, particularly in Cohort 4 (60 mg/day for 8 weeks). Inappropriately low cortisol responses to hypoglycemia were observed across cohorts at both baseline and Week 52, likely reflecting a combination of GSD Ia-associated hypocortisolism and steroid-induced adrenal suppression.

## 8.1.2.3 FDA Discussion

The efficacy findings from Phase 1/2 study are exploratory in nature with six protocol amendments. FDA determined that these findings cannot serve as confirmatory evidence to support the primary efficacy demonstrated in the Phase 3 study. The following limitations underline this determination:

- The single-arm adaptive design enrolled only 12 patients, of whom only 9 received a dose comparable to that used in the Phase 3 study. This limits the generalizability of the efficacy findings to the intended treatment population.
- The Phase 1/2 study enrolled adults exclusively, limiting direct comparability with the Phase 3 study population, which includes both pediatric and adult patients.

- The lack of a run-in period for nutritional and glycemic stabilization necessitated ongoing adjustments to cornstarch dosing and dietary carbohydrate content during the study, which confounded the interpretation of treatment effects.
- Other confounders such as physical activity and intercurrent illness, further limited the interpretability of efficacy results in the setting of the single arm design.
- The amendment lowering the controlled fasting challenge stopping threshold from  $\leq 60$  mg/dL to  $\leq 54$  mg/dL (Amendment 6, February 2021) introduced additional variability that complicated cross-cohort comparisons and overall efficacy interpretation.

These limitations underscore the necessity of a randomized, double-blind, controlled study to adequately evaluate the efficacy of DTX401. A critical component of such a design is pre-randomization nutritional optimization and confirmation of glycemic stability. This approach serves two intended purposes: it helps ensure that observed treatment effects are attributable to DTX401 rather than concurrent improvements in nutritional management, and it protects placebo-assigned subjects from hypoglycemia risk.

The safety findings are consistent with the safety profile characterized in the Phase 3 study, with no new safety signals identified beyond the following: Liver Enzyme Elevations, HPA Axis Suppression (Adrenal Insufficiency), and Metabolic Instability or Worsening. No clinically significant infusion reactions were reported.

Assessment of metabolic control served dual purposes: as an efficacy measure to evaluate treatment-related improvements in glycemic control and other metabolic parameters (e.g., triglycerides, lactic acid, and uric acid), and as a safety indicator to characterize disease-associated metabolic complications inherent to GSD1a.

### **8.1.3 Integrated Review of Effectiveness**

#### **8.1.4 Assessment of Efficacy Across Trials**

##### **8.1.4.1 Primary Endpoint**

###### Data:

Change in total daily cornstarch intake (primary endpoint in Phase 3) and change in additional cornstarch related endpoints including total daily cornstarch dose frequency and nighttime cornstarch across studies are presented in [Table](#).

**Table 30: Applicant – Cornstarch Intake and Dosing in Studies 401GSDIA01, 401GSDIA02 and DTX401-CL301**

| Statistic,<br>Mean<br>(SD)            | Weeks<br>after<br>DTX401<br>Treatment | 401GSDIA01/02<br>(Phase 1/2) | DTX401-CL301<br>(Phase 3) |                  |                                                      |
|---------------------------------------|---------------------------------------|------------------------------|---------------------------|------------------|------------------------------------------------------|
|                                       |                                       | Total<br>(N = 12)            | Placebo<br>(N = 23)       | DTX401<br>(N=19) | Crossover<br>Placebo→DTX401<br>(N = 19) <sup>a</sup> |
| Total Daily Cornstarch Intake         |                                       |                              |                           |                  |                                                      |
| Percent<br>change<br>from<br>Baseline | Week<br>52/48                         | -68 (19.5)                   | -10<br>(18.0)             | -41 (18.4)       | -61 (26.8)                                           |
|                                       | Week<br>104/96                        | -73 (19.6)                   | NA                        | -61 (19.7)       | -57 (1.7) <sup>b</sup>                               |
|                                       | Last Visit                            | -74 (22.6)                   | NA                        | -60 (20.7)       | -64 (23.4)                                           |
| Total Daily Cornstarch Dose Frequency |                                       |                              |                           |                  |                                                      |
| Change<br>from<br>Baseline            | Week<br>52/48                         | -2.4 (2.6)                   | -0.1<br>(0.6)             | -1.1 (0.9)       | -1.6 (1.9)                                           |
|                                       | Week<br>104/96                        | -2.8 (2.0)                   | NA                        | -1.9 (1.5)       | -2.0 (0.0) <sup>b</sup>                              |
|                                       | Last Visit                            | -3.4 (2.8)                   | NA                        | -2.0 (1.4)       | -1.8 (1.5)                                           |
| Nighttime Cornstarch Intake           |                                       |                              |                           |                  |                                                      |
| Percent<br>change<br>from<br>Baseline | Week<br>52/48                         | -87 (26.5)                   | +15<br>(103.5)            | -42 (29.2)       | -75 (26.2)                                           |
|                                       | Week<br>104/96                        | -100 (0.0)                   | NA                        | -70 (34.7)       | -100.0 (0.0) <sup>b</sup>                            |
|                                       | Last Visit                            | -79 (29.5)                   | NA                        | -68 (38.0)       | -75 (28.1)                                           |
| Nighttime Cornstarch Dose Frequency   |                                       |                              |                           |                  |                                                      |
| Change<br>from<br>Baseline            | Week<br>52/48                         | -1.3 (0.5)                   | +0.5<br>(1.3)             | -0.4 (0.6)       | -1.1 (1.7)                                           |
|                                       | Weeks<br>104/96                       | -1.3 (0.6)                   | NA                        | -0.8 (0.7)       | -1.0 (-) <sup>b</sup>                                |
|                                       | Last Visit                            | -1.0 (0.7)                   | NA                        | -0.9 (0.9)       | -1.2 (1.8)                                           |

<sup>a</sup> This column includes results for subjects who were in the Placebo group at Day 1 who crossed over and received DTX401 treatment at Week 48. Baseline for the Crossover Placebo→DTX401 group is the last observation prior to DTX401 dosing at Week 48.

<sup>b</sup> Data to be interpreted with caution as number of subjects is low.

Cells highlighted in grey indicate the results of the double-blind, placebo-controlled PEAP period of DTX401-CL301.

NA, not applicable; PEAP, Primary Efficacy Analysis Period.

Source: DTX401-CL301 Week 96 CSR Tables 14.2.1.1.1.1, 14.2.1.1.1.2, 14.2.1.2.1.1, 14.2.1.2.1.2, 14.2.1.2.2.2.1, 14.2.1.1.2.2.2, 14.2.1.2.2.2.2; 401GSDIA02 CSR Table 14.2.1.4

### Clinical Meaningfulness of Cornstarch Reductions Across Studies

- Across Studies 401GSDIA01, 401GSDIA02, and DTX401-CL301, subjects reporting improved GSDIa on the PGIC experienced substantial reductions in daily cornstarch intake. At Week 96 in Study DTX401-CL301, for the total sample (ie, Crossover Placebo→DTX401 group and DTX401 group combined), the average reduction in daily cornstarch intake was 68% for subjects reporting moderately/much improved (n = 17, collapsed response categories) GSDIa on the PGIC and 63% for subjects reporting any level of improvement (n = 26, collapsed categories) in GSDIa on the PGIC (DTX401-CL301 Week 96 CSR Table 14.2.1.4.3.3).
- At last available visit in Study 401GSDIA02, the average reduction in daily cornstarch intake was 63% for subjects reporting moderately/much improved (n = 5, collapsed response categories) GSDIa on the PGIC and 60% for subjects reporting any level of improvement (n = 6, collapsed categories) in GSDIa on the PGIC.
- During DTX401-CL301 Baseline interviews, each subject was asked to describe what would constitute a meaningful reduction in cornstarch intake. The mean desired reduction in cornstarch was 45% (median: 41%). Notably, of those reporting (n = 33), only 3 subjects (9%) reported that a 100% reduction would be meaningful, and 3 (9%) reported that any reduction would be meaningful (DTX401-CL301 Week 96 CSR Table 14.1.2.2.2.7).
- At Week 48, 83% (n = 10/12) of subjects in the DTX401 group met or exceeded their own Baseline-specified threshold for desired reduction in cornstarch intake compared to 15% (n = 3/20) of subjects in the Placebo group. Among all subjects who, at Week 48, exceeded their own Baseline expectation for desired cornstarch reduction (n = 9/32), mean reduction in cornstarch at Week 48 was 52%. Among all subjects who, at Week 48, met their own Baseline expectation for desired cornstarch reduction (n = 4/32, mean reduction in cornstarch at Week 48 was 34%. At Week 96, 77% of subjects (n = 20/26) with available data met or exceeded their own Baseline expectations for desired reduction in cornstarch intake (DTX401-CL301 Week 96 CSR Table 14.2.3.49.3, 14.2.3.49.4).
- Clinical meaningfulness was further evaluated in Study DTX401-CL301 by assessing responder analyses at Week 48 and Week 96 using pre-defined thresholds of meaningful cornstarch reductions (Section [8.1.1.6.8](#)).

The Applicant's Position:

***Evidence across studies consistently shows clinically meaningful and statistically significant cornstarch reductions with long-term durability of treatment effect that persists beyond 5 years.***

Studies 401GSDIA01, 401GSDIA02 and DTX401-CL301 unequivocally demonstrate that DTX401 treatment results in statistically significant and clinically meaningful sustained reductions in total daily cornstarch intake, total daily cornstarch dose frequency, nighttime cornstarch intake and nighttime dose frequency in subjects with GSDIa. While the magnitude of treatment effect was influenced by different study designs, these findings were consistently evident across 3 independent study periods, including the double-blind, placebo controlled DTX401-CL301 PEAP, the double-blind

DTX401-CL301 Crossover Period and the open-label 401GSDIA01/401GSDIA02 studies. The importance and relevance of a reduced cornstarch regimen, as evidenced in this research, was reinforced by findings from the recent Externally-led PFDD (EL-PFDD) on GSDIa convened by The Children’s Fund for GSD Research that called for therapies that reduce cornstarch intake to alleviate the profound burden of the condition.

**The FDA’s Assessment:**

Refer to Sections [8.1.1](#) and [8.1.2](#).

**8.1.4.2 Secondary and Other Endpoints**

**Data:**

[Table](#) summarizes the results across Study DTX401-CL301 and Studies 401GSDIA01 and 401GSDIA02 for secondary and tertiary endpoints providing totality of evidence of efficacy of DTX401 in GSDIa.

**Table 31: Applicant – Summary of Secondary and Other Endpoints Across Clinical Studies**

| Statistic,<br>Mean (SD)                                                | Weeks<br>after<br>DTX401<br>Treatment | 401GSDIA01/02<br>(Phase 1/2) | DTX401-CL301<br>(Phase 3) |                  |                                                      |
|------------------------------------------------------------------------|---------------------------------------|------------------------------|---------------------------|------------------|------------------------------------------------------|
|                                                                        |                                       | Total<br>(N = 12)            | Placebo<br>(N = 23)       | DTX401<br>(N=19) | Crossover<br>Placebo→DTX401<br>(N = 19) <sup>a</sup> |
| Percentage of Glucose Values in Hypoglycemic Range (< 70 mg/dL)        |                                       |                              |                           |                  |                                                      |
| Change<br>from<br>Baseline                                             | Week<br>52/48                         | +1.28 (1.77)                 | +0.11<br>(2.59)           | +3.12<br>(5.24)  | +2.44 (3.36)                                         |
|                                                                        | Weeks<br>104/96                       | +0.79 (0.67)                 | NA                        | +5.20<br>(6.32)  | -0.45 (0.64) <sup>b</sup>                            |
|                                                                        | Last Visit                            | NA                           | NA                        | +5.45<br>(6.52)  | +3.10 (5.88)                                         |
| Percentage of Glucose Values in Severe Hypoglycemic Range (< 54 mg/dL) |                                       |                              |                           |                  |                                                      |
| Change<br>from<br>Baseline                                             | Week<br>52/48                         | +0.08 (0.12)                 | +0.24<br>(0.71)           | +0.78<br>(1.19)  | +0.38 (0.69)                                         |
|                                                                        | Weeks<br>104/96                       | +0.06 (0.08)                 | NA                        | +1.24<br>(1.42)  | -0.65 (0.78) <sup>b</sup>                            |
|                                                                        | Last Visit                            | NA                           | NA                        | +1.00<br>(1.39)  | +0.53 (1.16)                                         |
| Percentage of Glucose Values in the 70 to 120 mg/dL Range              |                                       |                              |                           |                  |                                                      |
| Change<br>from<br>Baseline                                             | Week<br>52/48                         | +0.74 (2.09)                 | -6.48<br>(20.23)          | -2.91<br>(16.79) | +11.47 (15.88)                                       |
|                                                                        | Week<br>104/96                        | -1.09 (1.32)                 | NA                        | +8.87<br>(14.73) | +11.35 (22.70) <sup>b</sup>                          |
|                                                                        | Last Visit                            | NA                           | NA                        | +6.82<br>(17.92) | +11.21 (15.16)                                       |

| Statistic,<br>Mean (SD)                                                                                  | Weeks<br>after<br>DTX401<br>Treatment | 401GSDIA01/02<br>(Phase 1/2) | DTX401-CL301<br>(Phase 3) |                      |                                                      |
|----------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------|---------------------------|----------------------|------------------------------------------------------|
|                                                                                                          |                                       | Total<br>(N = 12)            | Placebo<br>(N = 23)       | DTX401<br>(N=19)     | Crossover<br>Placebo→DTX401<br>(N = 19) <sup>a</sup> |
| Fasting Tolerance During CFC, min/g                                                                      |                                       |                              |                           |                      |                                                      |
| Change<br>from<br>Baseline in<br>TTH<br>normalized<br>by amount<br>of<br>cornstarch<br>taken pre-<br>CFC | Week<br>52/48                         | +1.5 (20.40)                 | +2.8<br>(7.04)            | +12.8<br>(21.83)     | +25.79 (45.19)                                       |
|                                                                                                          | Week<br>104/96                        | +103.6 (120.94)              | NA                        | +19.3<br>(28.4)      | NA                                                   |
|                                                                                                          | Last Visit                            | +132.4 (265.72)              | NA                        | +18.13<br>(27.01)    | +43.87 (78.25)                                       |
| PGIC in GSDIa Since the Start of the Study                                                               |                                       |                              |                           |                      |                                                      |
| Mean<br>(SD),<br>Median                                                                                  | Week<br>52/48                         | 2.1 (1.2), 3.0               | 1.0<br>(1.1),<br>1.0      | 1.4<br>(1.4),<br>2.0 | 2.1 (1.0), 2.0                                       |
|                                                                                                          | Week<br>104/96                        | 2.1 (1.2), 3.0               | NA                        | 1.4<br>(1.2),<br>1.0 | 2.5 (0.7), 2.5 <sup>b</sup>                          |
|                                                                                                          | Last Visit                            | 1.8 (1.9), 2.5               | NA                        | 1.6<br>(1.5),<br>2.0 | 2.1 (0.9), 2.0                                       |
| Proportion of Subjects Reporting Improved GSDIa on PGIC                                                  |                                       |                              |                           |                      |                                                      |
| Percent<br>(n)                                                                                           | Week<br>52/48                         | 89 (8/9)                     | 52<br>(12/23)             | 79<br>(15/19)        | 95 (18/19)                                           |
|                                                                                                          | Week<br>104/96                        | 86 (6/7)                     | NA                        | 83<br>(10/12)        | 100 (2/2) <sup>b</sup>                               |

<sup>a</sup> This column includes results for subjects who were in the Placebo group at Day 1 who crossed over and received DTX401 treatment at Week 48. Baseline for the Crossover Placebo→DTX401 group is the last observation prior to DTX401 dosing at Week 48.

<sup>b</sup> Data to be interpreted with caution as number of subjects is low.

Cells highlighted in grey indicate the results of the double-blind, placebo-controlled PEAP period of DTX401-CL301.

CFC, controlled fasting challenge; CGM, continuous glucose monitoring; GSDIa, glycogen storage disease type Ia; NA, not applicable; PEAP, Primary Efficacy Analysis Period; PGIC, Patient Global Impression of Change.

Source: DTX401-CL301 Week 96 CSR Tables 14.2.1.3.1.1, Table 14.2.1.3.1.2, Table 14.2.1.3.2.1.2, Table 14.2.1.3.2.1.4, Table 14.2.1.7.1.1, Table 14.2.1.7.1.2, Table 14.2.1.6.2.1, Table 14.2.1.6.2.2; Study 401GSDIA02 CSR Tables 14.2.1.6.2, 14.2.1.2.1.

Applicant's Position:

Cumulative efficacy data across studies consistently demonstrate even with statistically significant, clinically meaningful and sustained reductions in cornstarch intake:

- Maintained low levels of hypoglycemia and improvements in glycemic control in the euglycemic range
- Improved fasting tolerance and protection against severe hypoglycemia in a CFC
- Shift from a cornstarch-dependent diet towards a more nutritionally balanced, food-based diet consistent with US Dietary Guidelines
- Improved patient experience, overall quality of life, and decreased burden of disease
- Persistence of treatment benefits beyond 5 years post-DTX401 (Section [8.1.4.3](#))

The FDA's Assessment:

Refer to Section [8.1.1.6.8](#).

### **8.1.4.2.1 Metabolic Control**

#### **Metabolic Control**

Data:

Metabolic control was assessed across several parameters in Studies 401GSDIA01, 401GSDIA02, DTX401-CL301 to evaluate metabolic parameters including lactate, triglyceride, uric acid and alanine levels which are commonly abnormal in GSDIa (Chou et al., 2015; van Schaftingen and Gerin, 2002; Chou, 2001).

Changes in lactate, uric acid and alanine were generally stable over time in Studies 401GSDIA01, 401GSDIA02 and DTX401-CL301 despite significant reductions in cornstarch following DTX401. In Study DTX401-CL301 PEAP, there was no statistically significant difference between the DTX401 and Placebo groups in the change from Baseline in lactate, uric acid and alanine (401GSDIA02 CSR Tables 14.2.1.3.1, 14.3.5.1.1, Listing 16.2.6.1.3; DTX401-CL301 Week 96 CSR Tables 14.2.3.18.1, 14.2.3.18.2, 14.2.3.12.1, 14.2.3.12.2, 14.2.3.10.1.1, 14.2.3.10.1.2).

In Study DTX401-CL301, increases in triglyceride levels were observed in the Placebo, DTX401 and Crossover Placebo→DTX401 groups, with larger increases observed following DTX401 (median triglyceride increase: 150-200 mg/dL) (DTX401-CL301 Week 96 CSR Tables 14.3.5.1.1.1, 14.3.5.1.1.2). Similar findings were observed in Study 401GSDIA01 and Study 401GSDIA02 (401GSDIA02 CSR Table 14.3.5.1.1). Generally, across studies, increases in triglycerides were observed within the first 48 weeks following DTX401 and then plateaued on longer term follow-up (DTX401-CL301 Week 96 CSR Figure 14.3.5.1.6, 401GSDIA02 CSR Figure 14.3.5.1.1). Across studies, in subjects with elevated triglycerides, there were no TEAEs of pancreatitis or clinical sequelae of atherosclerotic disease (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1, 401GSDIA02 CSR Listing 16.2.7.1.1).

Applicant's Position:

Overall metabolic control was stable after treatment with DTX401 although elevations in triglyceride levels were observed in a subset of subjects following DTX401. Hypertriglyceridemia is a common feature of GSDIa (>90% of patients; (Rake et al., 2002)) due to a complex underlying pathophysiology which is not fully understood and often challenging to manage. Elevations in triglycerides may reflect challenges to management with overtreatment/undertreatment of cornstarch and/or dietary carbohydrates in a clinical trial setting where experience with DTX401 management was evolving. Triglycerides will continue to be evaluated in the long-term follow-up of subjects in the GSDIa Disease Monitoring Program (DMP)

The FDA's Assessment:

Refer to Section [8.1.1.6.8](#), FDA Assessment, Table 25 Metabolic Parameters.

### **8.1.4.3 Persistence of Efficacy**

Data:

Persistence of DTX401 efficacy is primarily supported by long-term follow-up data from the Phase 1/2 Study 401GSDIA02 (Section [8.1.2.2](#) and last visit in [Table](#), [Table](#)) and additional supportive data from long term follow-up of subjects in Study DTX401-CL301 (Last visit data in Section [8.1.1.6.8](#), Section [8.1.1.6.10](#), Section [8.1.1.6.14](#), [Table](#), [Table](#)). As of the data cut for the 401GSDIA02 study for this dossier, the mean duration of follow-up was 4.9 years after DTX401 administration and up to 6 years. All 12 subjects have been followed for > 3.5 years, and 6 subjects have been followed for > 5 years (401GSDIA02 CSR Table 14.1.1.2).

Applicant's Position:

The available data from Study 401GSDIA02 demonstrates persistence of DTX401 efficacy >5 years post-dose. These data are supported by results at the last available visit of the Phase 3 study with a mean duration of follow-up of 1.8 years post-DTX401 administration, with maximum follow-up of 2.8 years (DTX401-CL301 Week 96 CSR Table 14.1.4. 1.2).

The FDA's Assessment:

FDA did not review the long-term follow-up data from the Phase 1/2 study, given the limitations described in Section [8.1.2](#).

### **8.1.4.4 Subpopulations**

Data:

Refer to Section [8.1.1.6.8](#) for subgroup analysis by age for reduction in cornstarch intake in Study DT401-CL301.

The FDA's Assessment:

FDA concurs with Applicant's subgroup analysis by age for reduction in cornstarch intake in Study DT401-CL301, presented in Section [8.1.1.6.8](#).

At Week 48 (PEAP), pediatric subjects in the DTX401 group showed smaller reductions in daily cornstarch intake compared to adults (35% vs. 46%). By Week 96, this gap narrowed, with pediatric subjects achieving greater reductions than adults (68% vs. 57%). In the Crossover Placebo→DTX401 group, cornstarch reductions were similarly across both age subgroups and substantially exceeded those observed during the PEAP, supporting a consistent treatment effect of DTX401 regardless of age.

On 6/4/2026, the FDA clinical team issued an Information Request (IR) asking the Applicant to identify a subgroup, defined by baseline demographics or characteristics, that demonstrated the greatest reduction in total daily and nighttime cornstarch (CS) intake, corroborated by patient-reported outcomes including PGIC assessments. If no such subgroup could be identified, the Applicant was asked to conduct a retrospective analysis of patients with the greatest reduction in uncooked cornstarch (UCCS) intake, incorporating metabolic parameter analysis and patient-reported outcomes as described above.

The Applicant was unable to identify a subgroup defined by baseline demographics or characteristics that demonstrated the greatest reduction in total daily and nighttime cornstarch intake.

### 8.1.5 Integrated Assessment of Effectiveness

#### Data:

***By addressing the underlying pathophysiology of GSDIa and establishing G6Pase activity, DTX401 enables statistically significant, clinically meaningful and sustained reductions in cornstarch***

#### **Statistically significant cornstarch reductions were achieved with DTX401:**

- Reductions in daily cornstarch intake were significantly greater with DTX401 than Placebo during the DTX401-CL301 PEAP meeting the primary endpoint of the Phase 3 study (Section [8.1.1.6.8](#)).
- Statistically significant improvements compared with Placebo were consistently observed across all cornstarch-related endpoints and highlight the substantial benefits of DTX401 treatment in reducing dependence on cornstarch required by GSDIa patients to avoid life-threatening hypoglycemia (Section [8.1.1.6.10](#)).
- The significant reductions in cornstarch dose frequency including at nighttime are particularly notable as typical patterns of cornstarch modifications in the management of GSDIa include a gradual reduction in the total amount of cornstarch intake, with reductions spread throughout the day before considering dose elimination, especially at night, to ensure glycemic stability.

#### **Greater magnitude of treatment effect was observed in the DTX401-CL301 Crossover Period and 401GSDIA01/401GSDIA02 studies, which more closely resemble a true-effect size than the DTX401-CL301 PEAP:**

- During the DTX401-CL301 Crossover Period, notably greater reductions across all cornstarch endpoints were observed in the Crossover Placebo→DTX401 group compared with both the Placebo and DTX401 groups within the same

timeframe post-treatment during the PEAP (Section [8.1.1.6.8](#) and Section [8.1.1.6.10](#)). The findings in the Crossover Placebo→DTX401 group are particularly important as this treatment group provides pre-DTX401 and post-DTX401 data in the same group of subjects (ie, Placebo group in the PEAP that crossed over to DTX401 at Week 48). Further, the positive treatment effects of DTX401 in this group during the Crossover Period were demonstrated relative to *Crossover Baseline*; ie, any improvements seen with DTX401 were on top of the first 48-weeks of the PEAP in which subjects were carefully managed in a clinical trial setting.

- In the Crossover Period, continued reductions in cornstarch were also observed on long-term follow-up for the DTX401 group.
- The magnitude of treatment effect in the DTX401-CL301 Crossover Period for both treatment groups was consistent with the 401GSDIA01 and 401GSDIA02 studies and suggest that when Investigators were confident subjects had received DTX401 treatment to establish G6Pase activity, they were able to more appropriately reduce daily cornstarch intake and dosing, resulting in a more pronounced treatment effect.

**Cornstarch reductions sustained > 5 years post-dose demonstrates durability of DTX401 treatment effect:**

- The positive impact of DTX401 treatment on cornstarch parameters persisted > 5 years post-DTX401 in the 401GSDIA02 extension study at last available follow-up (Section [8.1.4.3](#)). Further supportive data on durability is available in Study DTX401-CL301 with up to 3 years of follow-up (Section [8.1.4.3](#)).

**Cornstarch reductions enabled by DTX401 treatment were clinically meaningful to patients:**

- Clinical meaningfulness of cornstarch reductions was informed by Studies 401GSDIA01 and 401GSDIA02, published literature, patient concept elicitation interviews, patient and caregiver surveys, Ultragenyx-sponsored advisory boards, and FDA-sponsored patient listening sessions.
- In the DTX401-CL301 Baseline interviews, only 3 subjects (9%, n = 3/33) reported that a 100% reduction would be meaningful, and the mean desired reduction was 45%. Results at Weeks 48 and 96 far exceeded this threshold at the group level and a high proportion of DTX-treated participants met or exceeded this threshold at the participant level (Section [8.1.4.1](#)).
- In Study DTX401-CL301, responder analyses at Week 48 demonstrated that a statistically significant greater number of DTX401 treated than Placebo patients had reduced cornstarch by  $\geq 50\%$  (Section [8.1.4.1](#)).

***Appropriateness of cornstarch reductions was evidenced by totality of evidence including: maintained low levels of hypoglycemia and improvements in euglycemia, fasting tolerance, and quality of life which together address important treatment and management goals in GSDIa***

**Maintained low levels of hypoglycemia, improved euglycemia and improved fasting tolerance with DTX401 treatment:**

- DTX401 treatment enabled substantial reductions in cornstarch without clinically meaningful increases in hypoglycemia (< 70 mg/dL and < 54 mg/dL) and an overall improvement in euglycemia (70-120 mg/dL).
- CGM data from the 401GSDIA01 and 401GSDIA02 studies are limited, but overall, on long-term follow-up, severe hypoglycemia < 54 mg/dL remained low ([Table](#)).
- Improvements in fasting tolerance were evidenced by increases in normalized time to hypoglycemia (< 54 mg/dL) in the DTX401-CL301, 401GSDIA01 and 401GSDIA02 studies and were sustained through long-term follow-up > 5 years post-dose ([Table](#)). These results are indicative of the protective effects of DTX401 against severe hypoglycemia, where G6Pase activity is established to provide additional protection against rapid crashes in glucose levels to < 54 mg/dL.

#### **DTX401-treated patients experience improvements in their GSDIa and health-related quality of life along with decreased burden of disease**

- Improved GSDIa was consistently reported on the PGIC across all studies following treatment with DTX401. Patient interviews further supported these findings, with subjects reporting improvements in key disease parameters like blood sugar stability, less tiredness, less anxiety/worry, and improved physical function, social life, and overall quality of life. Subjects indicated satisfaction with DTX401 treatment and reduced regimen burden.
- The clinical meaningfulness of low levels of hypoglycemia, improved glucose control in the euglycemic range and increased fasting tolerance following DTX401 treatment were collectively evident in patient interviews across studies.

#### The Applicant's Position:

The efficacy data across studies demonstrate that a single dose of DTX401 resulted in statistically significant and clinically meaningful reductions in cornstarch intake and dose frequency, including at nighttime, with maintained low levels of hypoglycemia, improvements in euglycemia, fasting tolerance and patient experience along with the ability to transition to a nutritionally balanced food-based diet. These results were sustained over time demonstrating long-term durability and persistence of DTX401 treatment effect.

These data provide robust support for substantial and sustained clinical benefit of DTX401 treatment in adult and pediatric patients 8 years and older with GSDIa.

#### The FDA's Assessment:

The Applicant has provided substantial evidence of effectiveness to support accelerated approval of DTX401 using the reduction in total daily cornstarch intake at Week 48 as a surrogate endpoint reasonably likely to predict clinical benefit. This is based on a single adequate and well-controlled clinical investigation, Study DTX401-CL301, with confirmatory evidence.

Study DTX401-CL301 is an ongoing randomized, placebo-controlled, double-blind PEAP (Weeks 1 to 48) Phase 3 study with a crossover period (Week 48 to 96) assessing the efficacy of DTX401 in pediatric and adult patients with GSDIa. A total of

46 patients received a single intravenous infusion of DTX401 and were included in the primary efficacy analysis dataset.

DTX401 demonstrated a statistically significant reduction in daily cornstarch intake, with treated patients achieving a 41% reduction from baseline compared to 10% in the placebo group (LS mean difference:  $\sim$ –31 percentage points; 95% CI: –40.8%, –20.9%;  $p < 0.0001$ ), along with a reduction in daily dosing frequency of approximately one dose per day ( $p = 0.0004$ ).

CGM data showed that DTX401 reduced hyperglycemic exposure ( $>120$  mg/dL) relative to placebo (–2.8% vs. +6.5%; difference: –9.2%; 95% CI: –17.9%, –0.5%), reflecting a favorable downward shift in glucose distribution. Consistent with this, time in the optimal glycemic range (70–120 mg/dL) was better preserved in the DTX401 group relative to placebo (–0.51% vs. –6.54%; LS mean difference: +6.03%; 95% CI: –1.47%, 13.52%), suggesting a directionally favorable effect on glucose homeostasis, though this did not reach statistical significance. However, these favorable shifts were accompanied by a small increase in time spent in the hypoglycemic range ( $<70$  mg/dL; +3.0% vs. +0.1%; LS mean difference: +2.9%; 95% CI: 0.6%, 5.2%), with a similar directional trend observed for severe hypoglycemia ( $<54$  mg/dL; difference: +0.51%; 95% CI: –0.15%, 1.16%).

TTH during the CFC improved by 1.1 hours in the DTX401 group versus 0.5 hours in placebo; the between-group difference of 0.6 hours was small and not statistically significant (95% CI: –1.7, 2.9;  $p = 0.590$ ).

Metabolic parameters did not show expected improvements alongside reduced cornstarch intake, as DTX401-treated patients trended toward greater elevations in triglycerides relative to placebo.

The reduction in percent of cornstarch intake is considered a surrogate efficacy endpoint reasonably likely to predict long-term clinical benefit of sustained reductions in total daily cornstarch doses and improvements in fasting tolerance as assessed by TTH during the controlled fasting challenge (CFC). A Postmarketing Requirement (PMR), to be completed within 5 years post-approval will verify this benefit in Study DTX401-CL301 over a 2-year follow-up. The study will assess total daily cornstarch doses, fasting tolerance (TTH), nighttime cornstarch doses, biochemical markers (triglycerides, uric acid, and lactate), and clinician-reported assessments of overall health.

Confirmatory mechanistic evidence comes from in vivo pharmacology studies in 2-week-old glucose-6-phosphatase, catalytic subunit 1 (G6PC) (b) (4) mice (b) (4), a suitable animal model of GSDIa. Following IV administration of DTX401, dose-dependent improvements in hepatic G6Pase activity, fasting glucose, cholesterol and triglyceride levels, hepatomegaly, and nephromegaly were observed (see Section 5 of this memo for a discussion of nonclinical data).

## 8.2 Review of Safety

### The Applicant's Position:

Comprehensive safety data are available from 3 DTX401 clinical studies in adult and pediatric subjects with GSDIa ([Table 7](#)). The safety assessments and safety monitoring in the clinical studies were designed to comprehensively evaluate the safety of DTX401 in the treatment and management of patients with GSDIa, including risks associated with DTX401. The safety profile of DTX401 was adequately characterized by safety database of 40 subjects in the DTX401-CL301 study and supported by an additional 12 subjects from the Phase 1/2 study and long-term extension, for a total of 52 subjects dosed with DTX401.

#### The FDA's Assessment:

To facilitate a streamlined safety review, FDA has included the safety evaluation of Phase 3 Study DTX401-CL301 and a summary of safety summary for Study 401GSDIA01 in this section. The safety evaluation of Phase 1/2 Study 401GSDIA01 in Section [8.1.2](#).

### **8.2.1 Safety Review Approach**

#### The Applicant's Position:

The safety evaluation is based on comprehensive safety data from Phase 3 study DTX401-CL301 and Phase 1/2 studies 401GSDIA01 and 401GSDIA02.

For Study DTX401-CL301, safety analyses were based on the Safety Analysis Set (N = 46), which includes all enrolled subjects who were dosed with blinded IP (placebo or DTX401) during the study. Treatment-emergent adverse event (TEAE) data and relevant laboratory evaluations are presented for the "Placebo" and "DTX401" groups (study period: PEAP; N = 25 and N = 21, respectively), the "Crossover Placebo→DTX401" group (study period: Crossover and Follow-up period; N = 19), and the "DTX401: Day 1 + Week 48" (study period: PEAP, Crossover and Follow-up period, N = 40).

For Studies 401GSDIA01 and 401GSDIA02, safety analyses were based on the Full Analysis Set, comprised of all 12 subjects who enrolled and received a dose of DTX401 in Study 401GSDIA01; all 12 subjects subsequently enrolled in Study 401GSDIA02. Data from both studies are presented cumulatively. TEAE data and relevant laboratory evaluations are presented for "Cohorts 2-4" (subjects who received DTX401 at the registrational dose, N = 9) and "Cohorts 1-4" (subjects who received DTX401 at any dose, N = 12) ([Table](#)).

Exposure and TEAE data were pooled across studies DTX401-CL301, 401GSDIA01, and 401GSDIA02 and are presented for all 49 subjects who received DTX401 at the registrational dose ("DTX401 Registrational Dose" group), and for the 52 subjects who have been dosed with DTX401 across studies ("Total DTX401" group) ([Table](#)). These data were complemented with data from individual clinical studies including clinical laboratory evaluations and vital signs, physical findings, and other observations related to safety data which are presented separately for Phase 3 study (DTX401-CL301) and Phase 1/2 studies (401GSDIA01 and 401GSDIA02). Safety messaging and conclusions are primarily based on the findings in the DTX401 Registrational Dose group (N = 49) and supported by all subjects dosed with DTX401 (N = 52).

The Sponsor has identified the following significant adverse events for DTX401 based on nonclinical and clinical data, literature review and AAV gene therapy class effects. Important identified risks for DTX401 include IRRs and hepatic reactions (eg, increased aminotransferase levels). Important potential risks for DTX401 are based on known AAV gene therapy class effects and include insertional mutagenesis and malignancy, thrombotic microangiopathy (TMA), and dorsal root ganglion (DRG) and peripheral nerve effects. Hypertriglyceridemia is a potential risk for DTX401. Adrenal insufficiency is a potential risk of study-related procedures associated with corticosteroid administration.

#### The FDA's Assessment:

The safety review focused on data from the following two studies:

- Phase 3 Study DTX401-CL301: A randomized, double-blind, placebo-controlled (Week 48), cross over (week 48 to Week 96) study in pediatric and adult patients ( $\geq 8$  years), with follow-up extending to Week 144.
- Phase 1/2 Study 401GSDIA01: A single arm, open-label, dose-exploration study of adults with GSD1a, followed for 52 weeks.

The FDA reviewed all safety data contained in the BLA submission; the Applicant's responses to information requests, communicated during the BLA review.

Safety information from the long-term follow-up program for Phase 3 Study DTX401-CL301 subjects (Disease Monitoring Program, Study DTX401-CL401), the long-term follow-up Study 401GSDIA02 for Phase 1/2 Study 401GSDIA01, and the 90-Day Safety Update Report submitted on March 16, 2026, was also reviewed. A high-level summary is provided in the Integrated Summary of Safety (ISS) in Section [8.2.9](#).

## **8.2.2 Review of the Safety Database**

### **8.2.2.1 Overall Exposure**

#### Data:

In the DTX401 Registrational Dose group, the mean (SD) dose administered was  $6.5 (1.7) \times 10^{13}$  GC/kg ([Table](#)). The median duration of follow-up was 2.1 (range: 1.0 to 5.5) years for subjects in the DTX401 Registrational Dose group and 2.1 (range: 1.0 – 5.9) years for subjects in the Total DTX401 group (ISS Table 14.1.4.1).

Following DTX401 administration, all subjects in Study DTX401-CL301, except for 2 subjects who experienced serious IRRs, received prednisolone prophylactically, and 11 of 12 subjects in Study 401GSDIA01 received prednisone, administered reactively (Cohorts 1-3) or prophylactically (Cohort 4). The mean (SD) duration of exposure to corticosteroids was 88.7 (43.3) days in the DTX401 Registrational Dose group (ISS Tables 14.1.3.2, 14.1.4.2).

**Table 32: Applicant – Exposure to Investigational Product (Safety Analysis Set)**

|                                                                     | 401GSDIA01/02                      |                                     | DTX401-CL301                 |                             |                                                       |                                                        | DTX401<br>Registrational<br>Dose: 1.0 x<br>10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) | Total<br>DTX401<br>(N = 52)<br>n (%) |
|---------------------------------------------------------------------|------------------------------------|-------------------------------------|------------------------------|-----------------------------|-------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------|
|                                                                     |                                    |                                     | PEAP                         |                             | Crossover<br>Period +<br>Follow-up<br>Period          | PEAP +<br>Crossover<br>Period +<br>Follow-up<br>Period |                                                                                        |                                      |
|                                                                     | Cohorts<br>2-4<br>(N = 9)<br>n (%) | Cohorts<br>1-4<br>(N = 12)<br>n (%) | Placebo<br>(N = 25)<br>n (%) | DTX401<br>(N = 21)<br>n (%) | Crossover<br>Placebo →<br>DTX401<br>(N = 19)<br>n (%) | DTX401:<br>Day 1 +<br>Week 48<br>(N = 40)<br>n (%)     |                                                                                        |                                      |
| <b>Dose<br/>Administered (x<br/>10<sup>14</sup> GC)<sup>a</sup></b> |                                    |                                     |                              |                             |                                                       |                                                        |                                                                                        |                                      |
| n                                                                   | 9                                  | 12                                  | 25                           | 19 <sup>b</sup>             | 19                                                    | 38                                                     | 47                                                                                     | 50                                   |
| Mean (SD)                                                           | 4.8 (1.0)                          | 3.9 (1.8)                           | 0.0 (0.0)                    | 7.1 (1.6)                   | 6.6 (1.6)                                             | 6.9 (1.6)                                              | 6.5 (1.7)                                                                              | 6.2 (2.0)                            |
| Median                                                              | 5.0                                | 4.2                                 | 0.0                          | 7.4                         | 6.7                                                   | 6.8                                                    | 6.5                                                                                    | 6.5                                  |
| Min, Max                                                            | 3.4, 6.0                           | 1.1, 6.0                            | 0, 0                         | 4.5, 9.0                    | 3.2, 8.9                                              | 3.2, 9.0                                               | 3.2, 9.0                                                                               | 1.1, 9.0                             |
| <b>Total patient-<br/>years<br/>exposure</b>                        | 40.8                               | 58.4                                | 23.3                         | 19.7                        | 25.2                                                  | 73.3                                                   | 114.1                                                                                  | 131.7                                |

See Section [8.2.1](#) for description of the treatment groups presented.

<sup>a</sup> Dose administered calculated only for subjects who received a full dose of investigational product.

<sup>b</sup> In this group, the DTX401 dose administered could not be determined for 2 subjects who experienced IRRs.

GC, genome copies; IRR, infusion-related reaction; ISS, Integrated Summary of Safety; PEAP, Primary Efficacy Analysis Period

Source: ISS Tables 14.1.3.1, Table 14.1.4.1

### The FDA's Assessment:

FDA agrees with the Applicant's summary of overall exposure in the clinical program, as presented in Table, including the total number of patients and duration of exposure in the safety database.

**Safety Database:** Fifty-eight (58) subjects who received DTX401 or Placebo in two studies.

### **Study 401GSDIA01 (Phase 1/2)**

A total of 12 subjects received DTX401 and followed up for 52 weeks

- 3 subjects received DTX401 at  $2.0 \times 10^{12}$  GC/kg (Cohort 1)
- 9 subjects received DTX401 at  $6.0 \times 10^{12}$  GC/kg (Cohorts 2, 3, 4). This dose is equivalent to the Phase 3 dose as measured by qPCR, and confirmed by the FDA CMC team

### **Study DTX401-CL301 (Phase 3)**

- Placebo-Controlled Period (PEAP, Week1 to 48)
  - 21 subjects received DTX401 at  $1.0 \times 10^{13}$  GC/kg (measured by Droplet Digital PCR)
  - 25 subjects received matching placebo
- Crossover Period (Week 48 to Week 96), extending to Week 144
  - 17 subjects who received DTX401 in PEAP received placebo
  - 19 subjects (Placebo→DTX401 group) received DTX401 at  $1.0 \times 10^{13}$  GC/kg at Week 48

The safety review focuses primarily on data from the Primary Efficacy Analysis Population (PEAP) of Study DTX401-CL301, which includes all patients who received their assigned treatment (n=46). Comparative safety data between the DTX401 and placebo groups were used to inform section 6 of the USPI.

During the crossover (CO) period, 10 of the 46 patients did not receive treatment (DTX401 or placebo) for the reasons described below; of these, 4 continued to be followed for safety data collection. As the safety evaluation was based on observed data, crossover period safety information was considered supportive and was not used to inform the USPI.

- Six (6) patients from the placebo in PEAP who were assigned to receive DTX410 in cross over did not receive DTX410 due to patient/parent preference (n=2), elevated LFTs (n=1), and positive AAV antibody titers (n=3).
- Four (4) patients from the DTX401 in PEAP who were assigned to receive placebo in crossover (CO) did not receive placebo due to parental withdrawal of consent (n=1), chose not to be dosed (n=2), and was ineligible due to a serious infusion-related reaction (IRR) on Day 1 (n=1).

Safety data from Study 401GSDIA01 (Phase 1/2) were reviewed to provide context for the safety profile characterized in the Phase 3 study.

### 8.2.2.2 Relevant Characteristics of the Safety Population

#### Data:

Of the 49 subjects from the DTX401 Registrational Dose group, 29 subjects (59%) were male. The majority of subjects were White (46 subjects [94%]) and Not Hispanic or Latino (36 subjects [74%]). Median (min, max) age at the time of study enrollment was 21.0 (range: 8.0 – 42.0) years. Fifteen subjects (31%) were 8-17 years of age (of which 9 subjects were 8-12 years of age, and 6 subjects were 13-17 years of age) and 34 subjects (69%) were ≥ 18 years of age at the time of study consent (ISS Table 14.1.2.1).

Of the 49 subjects from the DTX401 Registrational Dose group, the most commonly reported medical history terms (in ≥ 10% of subjects) included gastrotomy (20 subjects [40.8%]), hypertriglyceridemia (13 subjects [26.5%]), hyperuricemia (11 subjects [22.4%]), anxiety and hypertension (each 10 subjects [20.4%]), vitamin D deficiency (9 subjects [18.4%]), hypoglycemia, attention deficit hyperactivity disorder, hepatomegaly and headache (each 8 subjects [16.3%]), nephrolithiasis (7 subjects [14.3%]), biopsy liver, depression, pain, seasonal allergy and hepatic adenoma (each 6 subjects [12.2%]), and tonsillectomy, blood cholesterol increased, blood triglycerides increased and constipation (each 5 subjects [10.2%]) (ISS Table 14.1.2.2).

#### The Applicant's Position:

Demographics and frequency of GSDIa comorbidities were mostly balanced across the Phase 1/2 and Phase 3 studies, except for age, reflecting the different age ranges enrolled in Studies 401GSDIA01 and 401GSDIA02 vs Study DTX401-CL301. The studies enrolled a representative population of patients with GSDIa who were likely to benefit from DTX401 treatment. Across studies, subjects presented with substantial burden of disease at Baseline.

#### The FDA's Assessment:

Demographic and baseline characteristics of the mITT population (n=46) for Phase 3 Study DTX401-CL301 are presented in Table 12 and Table 13 in Section [8.1.1](#).

### 8.2.2.3 Adequacy of the Safety Database

#### Data:

The safety database includes 52 subjects treated with DTX401 across Study DTX401-CL301 and Studies 401GSDIA01 and GSDIA02. Across all studies, subjects have been followed for a median of 2 years and up to 6 years in Study 401GSDIA02, contributing to nearly 132 patient-years of exposure overall (ISS Table 14.1.4.1, [Table](#)).

#### The Applicant's Position:

Consistent with health authority advice to maximize the size of the safety database by including at least 48 week data for subjects who initially receive placebo in the pivotal

clinical study, the safety database presented with this package exceeds this recommendation with inclusion of at least Week 96 data for all subjects in Study DTX401-CL301 (equivalent to at least 48 weeks of follow-up post-DTX401 administration in crossover subjects), as well as provision of a Day 90 safety update report inclusive of Week 132 safety data for all subjects in this study. Additionally, the safety experience in Phase 1/2 studies 401GSDIA01 and GSDIA02 is considered comparable to the pivotal study and provides long-term follow-up of up to 6 years.

Given the rarity of the disease, the Applicant considers the safety database to be adequate for the evaluation of the long-term safety of DTX401 in patients with GSDIa, and for the assessment of the benefit–risk profile of DTX401 in the intended target population.

The FDA's Assessment:

Refer to ISS Section [8.2.9](#).

### **8.2.3 Adequacy of Applicant's Clinical Safety Assessments**

#### **8.2.3.1 Issues Regarding Data Integrity and Submission Quality**

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the safety review. Compliance with Good Clinical Practices is discussed in Section [8.1.1.6.1](#).

The FDA's Assessment:

FDA did not identify any significant data integrity or submission quality issues. Some data inconsistencies were noted across the submitted documents, and clinical information requests were issued to explain and resolve these inconsistencies and obtain additional information necessary for a comprehensive safety review.

#### **8.2.3.2 Categorization of Adverse Event**

The Applicant's Position:

Adverse events (AEs) were analyzed by incidence, severity, and relatedness. For the Integrated Summary of Safety (ISS) summary tables, TEAEs were coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. In Studies 401GSDIA01 and 401GSDIA02 and Study DTX401-CL301, the severity of AEs was assessed by Investigator based on the most current version of Common Terminology Criteria for Adverse Events (CTCAE) and CTCAE version 5.0, respectively. AEs were summarized by subject incidence rates, therefore, in any tabulation, a subject contributed only once to the count for a given AE (SOC or PT). For summary by maximum severity grade, n represented the numbers of subjects who had maximum severity of TEAE of that grade and [E] represented total number of TEAEs any subject experienced at that grade.

For identification of significant TEAEs, the Sponsor either used a pre-specified MedDRA search strategy (Standardised MedDRA Queries [SMQs]) or a list of identified relevant PTs to capture the associated medical concepts. For identification of events of hepatic reactions, the Sponsor took a staged approach starting with a broad MedDRA search strategy to evaluate potential events of interest, then defined a subset of relevant hepatic reactions for DTX401 that included PTs of transaminases increased, ALT increased, and AST increased.

In the DTX401 studies, IRRs were defined as AEs with features of hypersensitivity with onset during the infusion or up to 6 hours after end of the infusion.

#### The FDA's Assessment:

Adverse events (AEs) were analyzed by incidence, severity, and relatedness. Treatment-emergent adverse events (TEAEs) were coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 24.1. AE severity was assessed using CTCAE version 5.0.

### **8.2.3.3 Routine Clinical Tests**

#### The Applicant's Position:

The clinical laboratory evaluations included clinical chemistry (including liver function test [LFTs]), hematology, urinalysis, estimated glomerular filtration rate (eGFR), and coagulation panel. Laboratory tests, including aminotransferase levels were closely monitored throughout the duration of the study due to the risk of hepatic reactions with AAV gene therapy. If a clinically significant change in the medical and scientific judgment of the Investigator or abnormal clinical laboratory evaluation was observed, including those that worsened from Baseline, it was recorded as an AE or serious adverse event (SAE), and additional blood samples could be taken.

Any clinically significant laboratory tests assessments associated with GSDIa were not to be reported as AEs, unless they were judged by the Investigator to be more severe than expected for the subject's condition. For clinical laboratory parameters with continuous results, values and changes from Baseline were summarized by study visit. For clinical laboratory parameters with categorical results, results were included in listings only. Severity of selected chemistry and hematology laboratory parameters were graded according to the version 5.0 of CTCAE where severity grading criteria are available.

For hematology, biochemistry, and coagulation laboratory data, the number and percentage of patients with abnormalities on treatment were analyzed for selected laboratory parameters with shift tables using CTCAE grades to compare baseline to the worst on-treatment value. Liver function parameters (eg, ALT, AST) were analyzed for the number and percentage of patients with abnormalities on treatment. Potential Hy's law events were defined as those patients with concurrent occurrence of AST or ALT  $\geq 3$ x upper limit of normal (ULN) and total bilirubin (TBL)  $\geq 2$ x ULN and alkaline phosphatase (ALP)  $< 2$ x ULN in the same assessment. Laboratory abnormalities were programmatically calculated using CTCAE grading or low/normal/high based on normal

ranges.

The FDA's Assessment:

FDA agrees with the Applicant's description as outlined in the clinical protocol.

## **8.2.4 Safety Results: DTX401-CL301 (Phase 3)**

### **8.2.4.1 Deaths**

Data/Applicant's Position:

No deaths have been reported in any subject who participated in DTX401 clinical studies ([Table 35](#)). Not applicable.

The FDA's Assessment:

FDA concurs with the Applicant's assessment.

### **8.2.4.2 Serious Adverse Events**

Data:

In the DTX401 Registrational Dose group, 26 subjects (53.1%) experienced at least 1 serious TEAE and a total of 55 serious TEAEs ([Table 35](#)), which all resolved or resolved with sequelae. The most common serious TEAEs included gastroenteritis viral (6 subjects [12.2%]), gastroenteritis and lactic acidosis (each 5 subjects [10.2%]), and hypertriglyceridemia (4 subjects [8.2%]) (ISS Table 14.3.1.5). A total of 5 subjects (10.2%) experienced 5 serious TEAE considered by the Investigator to be related to DTX401 (.). These included IRRs (PT: anaphylactic reaction), hypertriglyceridemia (each 2 subjects [4.1%]) and hyperlactacidemia (1 subject [2.0%]) (ISS Table 14.3.1.6). See [Table](#) for all serious TEAEs reported in ≥ 2 subjects in the Total DTX401 group.

Four subjects experienced 4 serious TEAEs of hypertriglyceridemia, including 2 serious TEAEs assessed as related to DTX401 by the Investigator, which are discussed in Section [8.2.4.5](#).

There were 3 additional serious, related TEAEs (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1):

- 2 serious TEAEs of IRR (PT: anaphylactic reaction) during Study DTX401-CL301, assessed as related to DTX401 by the Investigator and Sponsor.
- 1 serious TEAE of hyperlactacidemia during Study DTX401-CL301, assessed as related to DTX401 by the Investigator, and assessed as not related to DTX401 and related to prednisolone by the Sponsor, and confounded by other contributing factors including underlying GSDIa disease and increased creatinine due to fluid restriction.

There was 1 serious, Grade 4 (life-threatening) TEAE of multiple organ dysfunction during Study 401GSDIA02, with onset 3 years after DTX401 administration (401GSDIA02 CSR Listing 16.2.7.1.1). The event was assessed as not related to

DTX401 by the Investigator and Sponsor, and attributable to septic shock secondary to cholecystitis.

In Studies 401GSDIA01 and 401GSDIA02 Cohort 1, 3 additional subjects experienced 22 serious TEAEs, for a total of 29 subjects (55.8%) experiencing 77 serious TEAEs in the Total DTX401 group (Table 35). None of the additional 22 serious TEAEs were considered by the Investigator and Sponsor to be related to DTX401. In this group, the higher percentage of events was driven by a single subject who experienced a total of 19 serious TEAEs (with onset ranging from Study Day 56-2137), nearly all moderate (Grade 2) in severity, including 6 serious TEAEs of hypoglycemia (with onset ranging from Study Day 589-1588, occurring in the setting of infection, or physical exertion and attributed to underlying disease), and 4 serious TEAEs associated with metabolic instability and elevated lactic acid, and infections (401GSDIA02 CSR Listing 16.2.7.1.1).

The Applicant's Position:

Serious TEAEs occurred in approximately half of all subjects (26 [53%]) treated with the registrational dose of DTX401, including 5 subjects who experienced 5 serious events that were considered related to DTX401 by the Investigator. The serious related TEAEs included 2 IRRs, 2 events of hypertriglyceridemia and 1 event of hyperlactacidemia. Following the 2 serious IRRs, risk mitigations measures were implemented, after which no additional subjects experienced an IRR. Events of hypertriglyceridemia and hyperlactacidemia were not considered related to DTX401 by the Sponsor. These are known features of GSDIa and in patients who have significant changes in nutritional management such as low or excessive cornstarch or carbohydrate intake, increases in triglycerides and lactate can occur. Further, the event of hyperlactacidemia occurred concurrently with a serious event of adrenal insufficiency, and both events were considered related to prednisolone by the Investigator and Sponsor. Most commonly reported serious adverse events included viral gastroenteritis, gastroenteritis, and events associated with metabolic dysregulation (eg, hypoglycemia, hypertriglyceridemia, and lactic acidosis). Gastroenteritis is a common cause of hypoglycemia in patients with GSDIa due to a combination of decreased oral carbohydrate intake, impaired enteral absorption of carbohydrates, and higher energy demands (Kishnani et al., 2014) and may be more clinically serious in this patient population. Events associated with metabolic dysregulation are consistent with the known disease manifestations of GSDIa and can be more severe in this patient population due to the inherent inability to maintain glucose homeostasis and metabolic stability, particularly during periods of intercurrent illness. As such, these events are considered unrelated to DTX401 and attributable to underlying disease.

**Table 33: Applicant – Serious Treatment-emergent Adverse Events Occurring in ≥ 2 Subjects in the Total DTX401 (N = 52) Group by System Organ Class and Preferred Term (Safety Analysis Set)**

| System Organ Class<br>Preferred Term                               | 401GSDIA01/02                          |                                         | DTX401-CL301                     |                                 |                                                           |                                                        | DTX401<br>Registrational<br>Dose: 1.0 x<br>10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] | Total<br>DTX401<br>(N = 52)<br>n (%) [E] |
|--------------------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|---------------------------------|-----------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------|
|                                                                    |                                        |                                         | PEAP                             |                                 | Crossover<br>Period +<br>Follow-up<br>Period              | PEAP +<br>Crossover<br>Period +<br>Follow-up<br>Period |                                                                                            |                                          |
|                                                                    | Cohorts<br>2-4<br>(N = 9)<br>n (%) [E] | Cohorts<br>1-4<br>(N = 12)<br>n (%) [E] | Placebo<br>(N = 25)<br>n (%) [E] | DTX401<br>(N = 21)<br>n (%) [E] | Crossover<br>Placebo →<br>DTX401<br>(N = 19)<br>n (%) [E] | DTX401:<br>Day 1 +<br>Week 48<br>(N = 40)<br>n (%) [E] |                                                                                            |                                          |
| Subjects with At Least 1<br>Serious TEAE [Total<br>Number of TEAE] | 5 (55.6)<br>[18]                       | 8 (66.7)<br>[40]                        | 3 (12.0)<br>[4]                  | 8 (38.1)<br>[10]                | 9 (47.4) [12]                                             | 21 (52.5)<br>[37]                                      | 26 (53.1) [55]                                                                             | 29 (55.8)<br>[77]                        |
| <b>Metabolism and<br/>nutrition disorders</b>                      | 5 (55.6)<br>[5]                        | 6 (50.0)<br>[12]                        | 0                                | 3 (14.3)<br>[3]                 | 4 (21.1) [4]                                              | 8 (20.0)<br>[13]                                       | 13 (26.5) [18]                                                                             | 14 (26.9)<br>[25]                        |
| Lactic acidosis                                                    | 3 (33.3)<br>[3]                        | 3 (25.0)<br>[3]                         | 0                                | 1 (4.8)<br>[1]                  | 0                                                         | 2 (5.0) [3]                                            | 5 (10.2) [6]                                                                               | 5 (9.6) [6]                              |
| Hypertriglyceridaemia                                              | 1 (11.1)<br>[1]                        | 1 (8.3) [1]                             | 0                                | 0                               | 3 (15.8) [3]                                              | 3 (7.5) [3]                                            | 4 (8.2) [4]                                                                                | 4 (7.7) [4]                              |
| Hypoglycaemia                                                      | 1 (11.1)<br>[1]                        | 2 (16.7)<br>[7]                         | 0                                | 1 (4.8)<br>[1]                  | 0                                                         | 2 (5.0) [3]                                            | 3 (6.1) [4]                                                                                | 4 (7.7)<br>[10]                          |
| Metabolic disorder                                                 | 0                                      | 1 (8.3) [1]                             | 0                                | 0                               | 1 (5.3) [1]                                               | 1 (2.5) [1]                                            | 1 (2.0) [1]                                                                                | 2 (3.8) [2]                              |
| <b>Infections and<br/>infestations</b>                             | 3 (33.3)<br>[8]                        | 4 (33.3)<br>[11]                        | 2 (8.0) [2]                      | 2 (9.5)<br>[2]                  | 3 (15.8) [4]                                              | 8 (20.0)<br>[12]                                       | 11 (22.4) [20]                                                                             | 12 (23.1)<br>[23]                        |
| Gastroenteritis viral                                              | 1 (11.1)<br>[2]                        | 1 (8.3) [2]                             | 1 (4.0) [1]                      | 0                               | 3 (15.8) [3]                                              | 5 (12.5) [5]                                           | 6 (12.2) [7]                                                                               | 6 (11.5)<br>[7]                          |
| Gastroenteritis                                                    | 1 (11.1)<br>[1]                        | 1 (8.3) [1]                             | 0                                | 2 (9.5)<br>[2]                  | 0                                                         | 4 (10.0) [4]                                           | 5 (10.2) [5]                                                                               | 5 (9.6) [5]                              |
| COVID-19                                                           | 1 (11.1)<br>[1]                        | 2 (16.7)<br>[2]                         | 0                                | 0                               | 0                                                         | 0                                                      | 1 (2.0) [1]                                                                                | 2 (3.8) [2]                              |

| System Organ Class<br>Preferred Term   | 401GSDIA01/02                          |                                         | DTX401-CL301                     |                                 |                                                          |                                                        | DTX401<br>Registrational<br>Dose: 1.0 x<br>10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] | Total<br>DTX401<br>(N = 52)<br>n (%) [E] |
|----------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|---------------------------------|----------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------|
|                                        |                                        |                                         | PEAP                             |                                 | Crossover<br>Period +<br>Follow-up<br>Period             | PEAP +<br>Crossover<br>Period +<br>Follow-up<br>Period |                                                                                            |                                          |
|                                        | Cohorts<br>2-4<br>(N = 9)<br>n (%) [E] | Cohorts<br>1-4<br>(N = 12)<br>n (%) [E] | Placebo<br>(N = 25)<br>n (%) [E] | DTX401<br>(N = 21)<br>n (%) [E] | Crossover<br>Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] | DTX401:<br>Day 1 +<br>Week 48<br>(N = 40)<br>n (%) [E] |                                                                                            |                                          |
| Gastroenteritis<br>norovirus           | 1 (11.1)<br>[1]                        | 2 (16.7)<br>[2]                         | 0                                | 0                               | 0                                                        | 0                                                      | 1 (2.0) [1]                                                                                | 2 (3.8) [2]                              |
| <b>Gastrointestinal<br/>disorders</b>  | 0                                      | 2 (16.7)<br>[5]                         | 0                                | 0                               | 0                                                        | 1 (2.5) [1]                                            | 1 (2.0) [1]                                                                                | 3 (5.8) [6]                              |
| Abdominal pain                         | 0                                      | 2 (16.7)<br>[2]                         | 0                                | 0                               | 0                                                        | 0                                                      | 0                                                                                          | 2 (3.8) [2]                              |
| <b>Investigations</b>                  | 0                                      | 1 (8.3) [1]                             | 0                                | 0                               | 2 (10.5) [2]                                             | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 3 (5.8) [3]                              |
| Blood lactic acid<br>increased         | 0                                      | 1 (8.3) [1]                             | 0                                | 0                               | 1 (5.3) [1]                                              | 1 (2.5) [1]                                            | 1 (2.0) [1]                                                                                | 2 (3.8) [2]                              |
| <b>Renal and urinary<br/>disorders</b> | 1 (11.1)<br>[2]                        | 2 (16.7)<br>[3]                         | 0                                | 0                               | 0                                                        | 1 (2.5) [1]                                            | 2 (4.1) [3]                                                                                | 3 (5.8) [4]                              |
| Nephrolithiasis                        | 1 (11.1)<br>[2]                        | 2 (16.7)<br>[3]                         | 0                                | 0                               | 0                                                        | 0                                                      | 1 (2.0) [2]                                                                                | 2 (3.8) [3]                              |
| <b>Endocrine disorders</b>             | 0                                      | 0                                       | 0                                | 2 (9.5)<br>[2]                  | 0                                                        | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 2 (3.8) [2]                              |
| Adrenal insufficiency                  | 0                                      | 0                                       | 0                                | 2 (9.5)<br>[2]                  | 0                                                        | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 2 (3.8) [2]                              |
| <b>Immune system<br/>disorders</b>     | 0                                      | 0                                       | 0                                | 2 (9.5)<br>[2]                  | 0                                                        | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 2 (3.8) [2]                              |
| Anaphylactic reaction                  | 0                                      | 0                                       | 0                                | 2 (9.5)<br>[2]                  | 0                                                        | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 2 (3.8) [2]                              |

See Section [8.2.1](#) for description of the treatment groups presented.  
SOC rows represent all subjects and events [E] data.

COVID-19, coronavirus disease 2019; GC, genome copies; ISS, Integrated Summary of Safety; PEAP, Primary Efficacy Analysis Period; SOC, System Organ Class; TEAE, treatment-emergent adverse event  
 Source: ISS Table 14.3.1.5

### The FDA's Assessment

#### **DTX401-CL301 (Phase 3)**

Across all 40 patients who received DTX401, 21 during the PEAP and 19 during the crossover period, a total of 20 SAE events occurred in 16 patients.

During **the PEAP**, SAEs were more frequent in the DTX401 group than in the placebo group, with 8 of 21 patients (38.1%) reporting 10 SAEs, compared with 3 of 25 placebo patients (12.0%) experiencing 4 SAEs (viral gastroenteritis in 2 patients and neuroglycopenia in 1 patient).

[Table 34](#) summarizes the SAEs in the DTX401 treatment arm, along with narrative summaries and the reviewer's assessments.

**Table 34: FDA – Serious Adverse Event During PEAP**

| Subject ID                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | AE Preferred Term     | Onset (Days) | Duration (Days) | Severity | Outcome            | Causality*        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------|-----------------|----------|--------------------|-------------------|
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Anaphylactic reaction | 1            | 1               | Grade 3  | Recovered/resolved | Related to DTX401 |
| A 10-year-old male experienced chest pain/discomfort, vomiting, tachycardia, and urticarial rash approximately one minute after starting DTX401 infusion (received 6ml). The infusion was immediately discontinued. The patient was treated with oral ondansetron, oral acetaminophen, oral diphenhydramine, intravenous famotidine 20 mg, and normal saline 500 ml infusion. The patient continued in the study for safety follow-up and completed the 48-week PEAP. The patient was ultimately withdrawn from the study by their parent/guardian after 566 days of total study participation. |                       |              |                 |          |                    |                   |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Anaphylactic reaction | 1            | 2               | Grade 3  | Recovered/resolved | Related to DTX401 |
| A 14-year-old male developed dyspnea and hypoxia to saturation of 80% approximately 6 minutes after starting DTX401 infusion (received 14ml), followed by a rash. The infusion was discontinued and the event was treated with inhaled albuterol, intravenous diphenhydramine and hydrocortisone. The patient completed the 48-week PEAP follow-up and remains in the study for continued long-term safety follow-up as of the most recent data cutoff date.                                                                                                                                    |                       |              |                 |          |                    |                   |

| Subject ID                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | AE Preferred Term     | Onset (Days) | Duration (Days) | Severity | Outcome            | Causality*                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------|-----------------|----------|--------------------|------------------------------------------------------|
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Gastroenteritis       | 97           | 8               | Grade 3  | Recovered/resolved | Possibly related to steroid use# and GSD1a           |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Adrenal insufficiency | 97           | 35              | Grade 3  | Recovered/resolved | Possibly Related to steroid tapering and GSD1a       |
| <i>A 16-year-old male experienced 2 concurrent SAEs starting Day 97: (1) gastroenteritis and (2) adrenal insufficiency attributed to prednisolone with physiological stress from the concurrent infection.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                       |              |                 |          |                    |                                                      |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Hyperlacticaemia      | 48           | 3               | Grade 3  | Recovered/resolved | Possibly related to Steroid Use and GSD1a            |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Adrenal insufficiency | 59           | 19              | Grade 3  | Recovered/resolved | Related to Steroid tapering and GSD1a                |
| <i>This 17-year-old female developed hyperlactacidemia (lactate 12 mmol/L), with Cushingoid features (moon facies, dark skin, weakness) on Day 48 during the prednisolone taper. This resolved with IV fluids and she continued the prednisolone taper. On Day 59, she presented to the ER with hypoglycemia (glucose 55 mg/dL), metabolic/lactic acidosis (lactate 18.4 mmol/L, bicarbonate 10 mmol/L), hyponatremia (sodium 134 mmol/L), and hyperkalemia (potassium 5 mmol/L), consistent with adrenal insufficiency. Despite initial improvement, she deteriorated with hypotension, tachycardia, and hemodynamic instability requiring ICU transfer. She developed anuria (requiring high-dose diuretics), bilateral pleural effusion, and persistent vomiting with elevated lactate. Treatment included repeated hydrocortisone IV, IV fluids, and IV bicarbonate. She was discharged from ICU on Day 70 and from hospital on Day 77 on oral hydrocortisone 40 mg QID with continued taper.</i> |                       |              |                 |          |                    |                                                      |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Hypoglycemia          | 303          | 3               | Grade 2  | Recovered/resolved | Unlikely related                                     |
| <i>A 20-year-old female had hypoglycemia reported as an SAE approximately 10 months after DTX401, occurring in the context of a self-initiated reduction in cornstarch intake without medical guidance.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                       |              |                 |          |                    |                                                      |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Lactic acidosis       | 42           | 2               | Grade 2  | Recovered/resolved | Possibly related to Steroid Use and underlying GSD1a |
| <i>A 31-year-old male was hospitalized with lactic acidosis. He was admitted to hospital with symptoms of headache, increased stomach pain, and foot swelling about 4 weeks after starting prednisone course. His lactate level the day prior to DTX401 administration was 5.3mmol/L. His lactate peaked at 8.9 mmol/L.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                       |              |                 |          |                    |                                                      |
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Gastroenteritis       | 307          | 5               | Grade 3  | Recovered/resolved | Unclear.                                             |
| <i>An 11-year-old female was hospitalized for gastroenteritis approximately 10 months following DTX401 administration in the setting of sick contacts at school and home. The event was deemed unrelated to DTX401.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                       |              |                 |          |                    |                                                      |

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| Subject ID                                                                                                                                                                                                                                                                                                                              | AE Preferred Term              | Onset (Days) | Duration (Days) | Severity | Outcome            | Causality* |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------|-----------------|----------|--------------------|------------|
| (b) (6)                                                                                                                                                                                                                                                                                                                                 | Combined tibia-fibula fracture | 5            | 4               | Grade 3  | Recovered/resolved | Unrelated  |
| <i>A 28-year-old male sustained a traumatic fracture 4 days after DTX401 infusion in a skating accident. The event was assessed as unrelated to DTX401.</i>                                                                                                                                                                             |                                |              |                 |          |                    |            |
| Source: Reviewer<br>* FDA assessment.<br># Corticosteroid treatment is a concomitant treatment after DTX410 administration.<br>Abbreviations: ER, emergency room; GSD1a, Glycogen Storage Disease Type Ia; ICU, intensive care unit; ID, identifier; IV, intravenous; PEAP, Primary Efficacy Assessment Period; QID, four times per day |                                |              |                 |          |                    |            |

### **During the Crossover (Week 48 to Week 96) and Follow up Period (Through Week 144) (Placebo → DTX401, N=19)**

Nine of 19 patients (47.4%) in the Crossover Placebo→DTX401 group experienced 12 SAEs during the crossover and follow-up periods, of which 8 were Grade 3 in severity. All events resolved or resolved with sequelae. SAEs fell into the following categories:

- Infections (n=3 patients, 15.8%): Viral gastroenteritis (n=3 events) and influenza (n=1 event) were reported, all assessed as unrelated to DTX401 and consistent with intercurrent illness.
- Serious metabolic events (n=4 patients, 21.1%): Hypertriglyceridemia was the most common serious metabolic event, occurring in 3 pediatric patients (15.8%) and attributed to metabolic instability related to the underlying disease. Notably, the metabolic profile was not adequately controlled or improved following DTX401 treatment in these patients. One additional patient experienced serious blood lactic acid elevation.
- Transaminase elevation (n=1 patient, 5.3%): Grade 3 elevated transaminases were reported approximately 8 months post-DTX401 dosing, occurring concurrently with serious hypertriglyceridemia in the same patient.
- Neuroglycopenia (n=1 patient, 5.3%): One patient experienced a Grade 3 serious event of neuroglycopenia.

### **SAE Discussion**

The SAE profile across both periods reflects the interplay of three overlapping risk domains inherent to this patient population and DTX401 treatment and the concomitant corticosteroids treatment:

- DTX 401 treatment-attributable risks: Two safety signals were directly attributable to DTX401: anaphylactic reactions occurring within minutes of infusion, and transaminase elevation reflecting the hepatic immune response to AAV vector administration. Both warrants continued monitoring and appropriate labeling.
- Corticosteroid-related risks: Concomitant corticosteroid use, required to mitigate AAV-related hepatic toxicity, introduced additional risks including HPA axis suppression and worsened adrenal insufficiency, particularly dangerous in a population already predisposed to impaired cortisol counterregulation during metabolic stress. The severity of adrenal events observed, including one case requiring ICU admission, underscores the need for careful steroid management and baseline adrenal function screening.
- Disease-intrinsic risks: GSD1a patients are inherently predisposed to hypoglycemia, metabolic derangement (hyperlactatemia, lactic acidosis, hypertriglyceridemia), infection susceptibility due to functional neutrophil defects and innate immune dysfunction, and adrenal insufficiency. These risks were evident across both the PEAP and crossover periods and represent the baseline safety burden of the underlying condition.

### 8.2.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

Data/Applicant's Position:

There were no TEAEs leading to study discontinuation in any subject treated with DTX401 in any study ([Table](#)). Not applicable.

The FDA's Assessment:

FDA concurs with the Applicant's position.

### 8.2.4.4 Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data/Applicant's Position:

In the DTX401 Registrational Dose group, 2 subjects (4.1%) experienced 1 event each of IRR (PT: anaphylactic reaction) during the administration of DTX401 which resulted in immediate discontinuation of the infusion. See Section [8.2.4.5](#) for additional details.

The FDA's Assessment:

FDA concurs with the Applicant's position. Refer to Section of [8.2.4.2](#).

### 8.2.4.5 Significant Adverse Events

Data:

**IRRs (important identified risk for DTX401):** In the DTX401 Registrational Dose group, 2 subjects (4.1%) experienced 1 TEAE each of IRR (PT: anaphylactic reaction) (ISS Table 14.3.1.17). Both events occurred in Study DTX401-CL301 in the DTX401 group during the PEAP. Both events were serious and of severe (Grade 3) severity and resulted in immediate discontinuation of the infusion (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1). Symptoms included chest pain, single episode of vomiting, tachycardia, and urticarial rash in 1 subject, and coughing, difficulty breathing with decrease in oxygen saturation and reticular rash in the other subject. Hypotension was not reported in either subject, and while considered, epinephrine was not administered to treat the IRRs. Both serious events resolved with symptomatic treatment. Following the 2 serious IRRs, risk mitigation measures were implemented, and no additional IRRs were reported or identified (DTX401-CL301 Week 96 CSR Tables 14.1.3.1.2, 14.3.1.11.2.6.2.1).

**Hepatic reactions (important identified risk for DTX401):** In the DTX401 Registrational Dose group, most subjects (38 subjects [77.6%]) experienced at least 1 TEAE of hepatic reactions (ISS Table 14.3.1.15). Hepatic reactions TEAEs were mostly nonserious, mild (Grade 1) or moderate (Grade 2) in severity, transient and generally resolved or improved with corticosteroid treatment. There was 1 serious TEAE of transaminases increased in Study DTX401-CL301 in the Crossover Placebo→DTX401 group 8 months after DTX401 dosing. The event was assessed as not related to DTX401 by the Investigator and Sponsor and attributable to adjustments to standard of care/cornstarch treatment and assessed as related to study participation (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1).

**Insertional Mutagenesis and Malignancy, TMA and DRG and peripheral nerve effects (important potential risks for DTX401):** Thus far in DTX401 clinical studies, there have been no safety events indicative of insertional mutagenesis and malignancy, TMA or DRG and peripheral nerve effects, which are known class effects of AAV-based gene therapy (Module 2.7.4 Section 2.1.9).

**Hypertriglyceridemia (potential risk for DTX401):** In the DTX401 Registrational Dose group, 23 subjects (46.9%) experienced TEAEs of hypertriglyceridemia (ISS Table 14.3.1.22). Four subjects experienced 4 serious TEAEs of hypertriglyceridemia of moderate (Grade 2; 1 event), severe (Grade 3; 2 events) and life-threatening (Grade 4; 1 event) severity requiring hospitalization for monitoring of metabolic laboratory parameters and diet and cornstarch adjustments. Two of the serious events were assessed as related to DTX401 by the Investigator. All 4 serious TEAEs of hypertriglyceridemia were assessed as unrelated to DTX401 by the Sponsor, and due to either history of hyperlipidemia and associated complications, underlying GSDIa, viral infections, or low or excessive cornstarch or carbohydrate intake (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1, 401GSDIA02 Listing 16.2.7.1.1).

**Adrenal insufficiency (potential risk of study-related procedures associated with corticosteroid use):** In the DTX401 Registrational Dose group, 7 subjects (14.3%) experienced 10 TEAEs associated with adrenal insufficiency (ISS Table 14.3.1.18), all of which occurred during administration of the immunomodulatory regimen. The events were serious in 2 subjects. The subjects who had nonserious events were based solely on low cortisol and low adrenocorticotrophic hormone (ACTH) values with no clinical signs or symptoms of adrenal insufficiency. Across studies, the time of onset of these events ranged from Study Day 28-97 (for 1 additional event, onset date was not specified). At the time of event onset, all subjects received corticosteroids per protocol (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1, 401GSDIA02 Listing 16.2.7.1.1).

The Applicant's Position:

DTX401 showed an acceptable safety profile. Identified adverse drug reactions (ADRs, [Table](#)) and risks are manageable through risk mitigation strategies which have been incorporated in the proposed label. The 2 events of IRRs resulted in early termination of the infusion and resolved on the same day with medications. Risk minimization measures were incorporated into the study protocol following occurrence of the IRR events and included a slower starting infusion rate with gradual increased rates, premedication, close monitoring of subjects during and after the infusion and further guidance to Investigators on management of IRRs. Following implementation of these measures, 17 subjects were dosed with DTX401, and there were no further IRRs reported or identified.

TEAEs associated with elevations in liver transaminases were the most frequently occurring TEAEs, and the most frequently reported DTX401-related events and are consistent with other clinical studies of AAV-mediated gene transfer across multiple indications. These elevations were effectively managed with prophylactic or reactive oral corticosteroids. No events met criteria for Hy's Law.

TEAEs of hypertriglyceridemia were observed in DTX401-treated subjects, and hypertriglyceridemia is considered a potential risk of DTX401 treatment. Hypertriglyceridemia is a known and common complication of GSDIa and the etiology is multifactorial; elevations and fluctuations in triglyceride levels were observed in subjects post DTX401 administration and may represent challenges to metabolic control following cornstarch and dietary adjustments.

Across AAV gene therapies including DTX401, corticosteroids are used prophylactically and reactively as needed, to mitigate for anticipated hepatic reactions. Adrenal insufficiency is considered a potential risk of study-related procedures associated with corticosteroid administration. After risk minimization measures were implemented to increase monitoring during steroid treatment, no further serious events of adrenal insufficiency have been reported.

#### The FDA's Assessment:

Refer to Section [8.2.4.5](#) for summary and discussion of TEAEs and Adverse Event of Special Interest (AESI).

#### **8.2.4.6 Treatment-Emergent Adverse Events and Adverse Reactions**

##### Data:

An overview of TEAEs reported during Studies 401GSDIA01 and 401GSDIA02 and Study DTX401-CL301 is provided in [Table](#).

TEAEs occurring in  $\geq 4$  subjects in the Total DTX401 group (which corresponds to approximately 8% of all subjects treated with DTX401), are presented by SOC and PT. To enable side by side presentation of TEAEs of all grades and the subset of Grade 3/4 only, events are presented for the DTX401-CL301 Placebo, DTX401, and Crossover Placebo→ DTX401 groups, and for the DTX401 Registrational Dose group ([Table 36](#)).

ADRs for DTX401 are presented in [Table](#).

##### The Applicant's Position:

The most frequently occurring TEAEs were associated with elevations in liver transaminases. See Section [8.2.4.5](#) for the Applicant Position.

To inform the DTX401 safety profile, all reported TEAEs, independent of dose and Investigator causality assessment, were medically reviewed for biological plausibility, temporal relationship to treatment, severity, seriousness, duration, and alternate etiologies and confounders (eg, underlying and intercurrent illness or concomitant medications).

A medical assessment of all TEAEs for the ISS Safety Analysis Set was performed with focus on important risks, TEAEs with onset within 1 day and up to 14 days after DTX401 administration (prior to corticosteroid administration), TEAEs occurring in the placebo-controlled portion of Study DTX401-CL301 (Week 48 PEAP), and TEAEs that may represent the European Medicines Agency Important Medical Events list and

considering multiple causality methods (eg, World Health Organization, Council for International Organizations of Medical Sciences). TEAEs temporally associated with corticosteroid use and established side effects of corticosteroids were not considered as ADRs for DTX401. TEAEs deemed to have at least a reasonable possibility of a causal relationship to DTX401, regardless of the Investigator's causality assessment, are considered ADRs.

Adverse reaction rates in Table were derived from all reported adverse events of that type based on all subjects (N = 52) exposed to DTX401 from the pooled data (ISS) across studies regardless of Investigator causality assessment.

**Table 35: Applicant – Overview of Treatment-emergent Adverse Events (Safety Analysis Set)**

|                                 | 401GSDIA01/02                          |                                         | DTX401-CL301                     |                                 |                                                          |                                                        | DTX401<br>Registrational<br>Dose: 1.0 x<br>10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] | Total<br>DTX401<br>(N = 52)<br>n (%) [E] |
|---------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|---------------------------------|----------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------|
|                                 |                                        |                                         | PEAP                             |                                 | Crossover<br>Period +<br>Follow-up<br>Period             | PEAP +<br>Crossover<br>Period +<br>Follow-up<br>Period |                                                                                            |                                          |
|                                 | Cohorts<br>2-4<br>(N = 9)<br>n (%) [E] | Cohorts<br>1-4<br>(N = 12)<br>n (%) [E] | Placebo<br>(N = 25)<br>n (%) [E] | DTX401<br>(N = 21)<br>n (%) [E] | Crossover<br>Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] | DTX401:<br>Day 1 +<br>Week 48<br>(N = 40)<br>n (%) [E] |                                                                                            |                                          |
| TEAEs                           | 9 (100.0)<br>[275]                     | 12<br>(100.0)<br>[433]                  | 22 (88.0)<br>[218]               | 21<br>(100.0)<br>[325]          | 19 (100.0)<br>[385]                                      | 40 (100.0)<br>[948]                                    | 49 (100.0)<br>[1223]                                                                       | 52 (100.0)<br>[1381]                     |
| Related TEAEs                   |                                        |                                         |                                  |                                 |                                                          |                                                        |                                                                                            |                                          |
| IP Related <sup>a</sup>         | 9 (100.0)<br>[71]                      | 12<br>(100.0)<br>[85]                   | 8 (32.0)<br>[48]                 | 16 (76.2)<br>[62]               | 14 (73.7)<br>[46]                                        | 31 (77.5)<br>[117]                                     | 40 (81.6) [188]                                                                            | 43 (82.7)<br>[202]                       |
| Prednisolone/Placebo<br>Related | 0                                      | 0                                       | 6 (24.0)<br>[13]                 | 15 (71.4)<br>[111]              | 15 (78.9)<br>[64]                                        | 30 (75.0)<br>[180]                                     | 30 (61.2) [180]                                                                            | 30 (57.7)<br>[180]                       |
| Study Participation<br>Related  | 0                                      | 0                                       | 7 (28.0)<br>[14]                 | 3 (14.3)<br>[3]                 | 10 (52.6)<br>[58]                                        | 20 (50.0)<br>[81]                                      | 20 (40.8) [81]                                                                             | 20 (38.5)<br>[81]                        |
| Serious TEAEs                   | 5 (55.6)<br>[18]                       | 8 (66.7)<br>[40]                        | 3 (12.0)<br>[4]                  | 8 (38.1)<br>[10]                | 9 (47.4)<br>[12]                                         | 21 (52.5)<br>[37]                                      | 26 (53.1) [55]                                                                             | 29 (55.8)<br>[77]                        |
| Serious Related TEAEs           |                                        |                                         |                                  |                                 |                                                          |                                                        |                                                                                            |                                          |
| IP Related <sup>a</sup>         | 1 (11.1)<br>[1]                        | 1 (8.3) [1]                             | 0                                | 3 (14.3)<br>[3]                 | 1 (5.3) [1]                                              | 4 (10.0) [4]                                           | 5 (10.2) [5]                                                                               | 5 (9.6) [5]                              |
| Prednisolone/Placebo<br>Related | 0                                      | 0                                       | 0                                | 3 (14.3)<br>[4]                 | 0                                                        | 3 (7.5) [4]                                            | 3 (6.1) [4]                                                                                | 3 (5.8) [4]                              |
| Study Participation<br>Related  | 0                                      | 0                                       | 0                                | 0                               | 3 (15.8) [4]                                             | 3 (7.5) [4]                                            | 3 (6.1) [4]                                                                                | 3 (5.8) [4]                              |
| TEAE with Maximum<br>Severity   |                                        |                                         |                                  |                                 |                                                          |                                                        |                                                                                            |                                          |

|                                           | 401GSDIA01/02                          |                                         | DTX401-CL301                     |                                 |                                                           |                                                        | DTX401<br>Registrational<br>Dose: 1.0 x<br>10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] | Total<br>DTX401<br>(N = 52)<br>n (%) [E] |
|-------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|---------------------------------|-----------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------|
|                                           |                                        |                                         | PEAP                             |                                 | Crossover<br>Period +<br>Follow-up<br>Period              | PEAP +<br>Crossover<br>Period +<br>Follow-up<br>Period |                                                                                            |                                          |
|                                           | Cohorts<br>2-4<br>(N = 9)<br>n (%) [E] | Cohorts<br>1-4<br>(N = 12)<br>n (%) [E] | Placebo<br>(N = 25)<br>n (%) [E] | DTX401<br>(N = 21)<br>n (%) [E] | Crossover<br>Placebo →<br>DTX401<br>(N = 19)<br>n (%) [E] | DTX401:<br>Day 1 +<br>Week 48<br>(N = 40)<br>n (%) [E] |                                                                                            |                                          |
| Grade 5                                   | 0                                      | 0                                       | 0                                | 0                               | 0                                                         | 0                                                      | 0                                                                                          | 0                                        |
| Grade 4                                   | 2 (22.2)<br>[4]                        | 2 (16.7)<br>[4]                         | 0                                | 0                               | 0                                                         | 0                                                      | 2 (4.1) [4]                                                                                | 2 (3.8) [4]                              |
| Grade 3                                   | 3 (33.3)<br>[7]                        | 4 (33.3)<br>[8]                         | 5 (20.0)<br>[12]                 | 8 (38.1)<br>[14]                | 9 (47.4)<br>[16]                                          | 25 (62.5)<br>[49]                                      | 28 (57.1) [56]                                                                             | 29 (55.8)<br>[57]                        |
| Grade 2                                   | 3 (33.3)<br>[39]                       | 5 (41.7)<br>[76]                        | 9 (36.0)<br>[60]                 | 10 (47.6)<br>[71]               | 9 (47.4)<br>[104]                                         | 13 (32.5)<br>[220]                                     | 16 (32.7) [259]                                                                            | 18 (34.6)<br>[296]                       |
| Grade 1                                   | 1 (11.1)<br>[225]                      | 1 (8.3)<br>[345]                        | 8 (32.0)<br>[146]                | 3 (14.3)<br>[240]               | 1 (5.3)<br>[265]                                          | 2 (5.0)<br>[679]                                       | 3 (6.1) [904]                                                                              | 3 (5.8)<br>[1024]                        |
| Grade 3 or 4 TEAEs                        | 5 (55.6)<br>[11]                       | 6 (50.0)<br>[12]                        | 5 (20.0)<br>[12]                 | 8 (38.1)<br>[14]                | 9 (47.4)<br>[16]                                          | 25 (62.5)<br>[49]                                      | 30 (61.2) [60]                                                                             | 31 (59.6)<br>[61]                        |
| Grade 3 or 4 Related<br>TEAEs             |                                        |                                         |                                  |                                 |                                                           |                                                        |                                                                                            |                                          |
| IP Related <sup>a</sup>                   | 1 (11.1)<br>[3]                        | 1 (8.3) [3]                             | 1 (4.0)<br>[6]                   | 4 (19.0)<br>[4]                 | 3 (15.8) [5]                                              | 7 (17.5) [9]                                           | 8 (16.3) [12]                                                                              | 8 (15.4)<br>[12]                         |
| Prednisolone/Placebo<br>Related           | 0                                      | 0                                       | 0                                | 3 (14.3)<br>[5]                 | 2 (10.5) [2]                                              | 5 (12.5) [7]                                           | 5 (10.2) [7]                                                                               | 5 (9.6) [7]                              |
| Study Participation<br>Related            | 0                                      | 0                                       | 2 (8.0)<br>[3]                   | 0                               | 2 (10.5) [3]                                              | 3 (7.5) [4]                                            | 3 (6.1) [4]                                                                                | 3 (5.8) [4]                              |
| TEAEs leading to study<br>discontinuation | 0                                      | 0                                       | 0                                | 0                               | 0                                                         | 0                                                      | 0                                                                                          | 0                                        |

|                                                      | 401GSDIA01/02                          |                                         | DTX401-CL301                     |                                 |                                                           |                                                        | DTX401<br>Registrational<br>Dose: 1.0 x<br>10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] | Total<br>DTX401<br>(N = 52)<br>n (%) [E] |
|------------------------------------------------------|----------------------------------------|-----------------------------------------|----------------------------------|---------------------------------|-----------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------|
|                                                      |                                        |                                         | PEAP                             |                                 | Crossover<br>Period +<br>Follow-up<br>Period              | PEAP +<br>Crossover<br>Period +<br>Follow-up<br>Period |                                                                                            |                                          |
|                                                      | Cohorts<br>2-4<br>(N = 9)<br>n (%) [E] | Cohorts<br>1-4<br>(N = 12)<br>n (%) [E] | Placebo<br>(N = 25)<br>n (%) [E] | DTX401<br>(N = 21)<br>n (%) [E] | Crossover<br>Placebo →<br>DTX401<br>(N = 19)<br>n (%) [E] | DTX401:<br>Day 1 +<br>Week 48<br>(N = 40)<br>n (%) [E] |                                                                                            |                                          |
| TEAEs leading to<br>discontinuation of study<br>drug | 0                                      | 0                                       | 0                                | 2 (9.5) [2]                     | 0                                                         | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 2 (3.8) [2]                              |
| TEAEs leading to<br>infusion interruption            | 0                                      | 0                                       | 1 (4.0)<br>[1]                   | 0                               | 2 (10.5) [2]                                              | 2 (5.0) [2]                                            | 2 (4.1) [2]                                                                                | 2 (3.8) [2]                              |
| TEAEs leading to death                               | 0                                      | 0                                       | 0                                | 0                               | 0                                                         | 0                                                      | 0                                                                                          | 0                                        |

See Section [8.2.1](#) for description of the treatment groups presented.

<sup>a</sup> "IP Related" reflects events assessed as related to DTX401 in the single-arm Studies 401GSDIA01 and 401GSDIA02, or related to DTX401/placebo during the PEAP and Crossover Period in the controlled Study DTX401-CL301. Events related to prednisolone/placebo or study participation were only collected in Study DTX401-CL301, hence not applicable to Studies 401GSDIA01 and 401GSDIA02. In the description of the results, relatedness is presented based on actual treatment assignment post unblinding.

GC, genome copies; IP, investigational product; ISS, Integrated Summary of Safety; PEAP, Primary Efficacy Analysis Period; TEAE, treatment-emergent adverse event

Source: ISS Tables 14.3.1.1, 14.3.1.16, 14.3.1.18, 14.3.1.22

**Table 36: Applicant – Incidence of Treatment-emergent Adverse Events Reported by System Organ Class and Preferred Term for TEAEs Occurring in ≥ 4 Subjects in the Total DTX401 (N = 52) Group – All Grades vs Grade 3 and Grade 4 Events (Safety Analysis Set)**

| System Organ Class<br>Preferred Term                       | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                   |
|------------------------------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------|
|                                                            | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                   |
|                                                            | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                   |
|                                                            | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> |                                                                                         |                   |
| Subjects with at Least 1<br>TEAE [Total Number of<br>TEAE] | 21 (84.0)<br>[124]               | 5 (20.0)<br>[12]              | 19 (90.5)<br>[192]              | 8 (38.1) [14]                 | 19 (100.0)<br>[270]                                   | 9 (47.4)<br>[16]              | 48 (98.0)<br>[787]                                                                      | 30 (61.2)<br>[60] |
| <b>Investigations</b>                                      | 8 (32.0)<br>[21]                 | 0                             | 15 (71.4)<br>[43]               | 1 (4.8) [1]                   | 17 (89.5)<br>[81]                                     | 4 (21.1) [5]                  | 44 (89.8)<br>[184]                                                                      | 6 (12.2)<br>[8]   |
| Transaminases<br>increased                                 | 3 (12.0)<br>[6]                  | 0                             | 13 (61.9)<br>[19]               | 1 (4.8) [1]                   | 14 (73.7)<br>[29]                                     | 3 (15.8) [3]                  | 29 (59.2)<br>[56]                                                                       | 4 (8.2) [4]       |
| Alanine<br>aminotransferase<br>increased                   | 0                                | 0                             | 4 (19.0)<br>[8]                 | 0                             | 6 (31.6) [11]                                         | 2 (10.5) [2]                  | 16 (32.7)<br>[35]                                                                       | 2 (4.1) [2]       |
| GGT increased                                              | 3 (12.0)<br>[4]                  | 0                             | 4 (19.0)<br>[5]                 | 0                             | 9 (47.4) [12]                                         | 0                             | 15 (30.6)<br>[21]                                                                       | 0                 |
| Blood lactic acid<br>increased                             | 4 (16.0)<br>[7]                  | 0                             | 3 (14.3)<br>[4]                 | 0                             | 4 (21.1) [5]                                          | 0                             | 9 (18.4)<br>[11]                                                                        | 0                 |
| Blood creatine<br>phosphokinase<br>increased               | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 0                             | 2 (10.5) [4]                                          | 0                             | 9 (18.4)<br>[15]                                                                        | 1 (2.0) [2]       |
| Weight decreased                                           | 0                                | 0                             | 1 (4.8) [1]                     | 0                             | 4 (21.1) [4]                                          | 0                             | 9 (18.4)<br>[9]                                                                         | 0                 |
| Aspartate<br>aminotransferase<br>increased                 | 0                                | 0                             | 2 (9.5) [2]                     | 0                             | 2 (10.5) [3]                                          | 0                             | 7 (14.3)<br>[11]                                                                        | 0                 |
| Blood triglycerides<br>increased                           | 1 (4.0) [1]                      | 0                             | 2 (9.5) [2]                     | 0                             | 5 (26.3) [6]                                          | 0                             | 7 (14.3)<br>[8]                                                                         | 0                 |

| System Organ Class<br>Preferred Term                  | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                               |
|-------------------------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|
|                                                       | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                               |
|                                                       | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                               |
|                                                       | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                                                                           | Grade 3<br>and 4 <sup>a</sup> |
| Activated partial<br>thromboplastin time<br>prolonged | 0                                | 0                             | 0                               | 0                             | 2 (10.5) [3]                                          | 0                             | 6 (12.2)<br>[7]                                                                         | 0                             |
| Blood uric acid<br>increased                          | 2 (8.0) [2]                      | 0                             | 1 (4.8) [1]                     | 0                             | 2 (10.5) [2]                                          | 0                             | 6 (12.2)<br>[6]                                                                         | 0                             |
| Blood glucose<br>fluctuation                          | 0                                | 0                             | 0                               | 0                             | 2 (10.5) [2]                                          | 0                             | 4 (8.2) [5]                                                                             | 0                             |
| Infections and<br>infestations                        | 16 (64.0)<br>[37]                | 2 (8.0) [2]                   | 17 (81.0)<br>[36]               | 2 (9.5) [2]                   | 14 (73.7)<br>[58]                                     | 2 (10.5) [2]                  | 40 (81.6)<br>[155]                                                                      | 8 (16.3)<br>[13]              |
| Upper respiratory<br>tract infection                  | 4 (16.0)<br>[4]                  | 0                             | 6 (28.6)<br>[9]                 | 0                             | 4 (21.1) [4]                                          | 0                             | 17 (34.7)<br>[26]                                                                       | 0                             |
| COVID-19                                              | 4 (16.0)<br>[4]                  | 0                             | 4 (19.0)<br>[4]                 | 0                             | 3 (15.8) [4]                                          | 0                             | 14 (28.6)<br>[18]                                                                       | 0                             |
| Gastroenteritis viral                                 | 4 (16.0)<br>[4]                  | 1 (4.0) [1]                   | 1 (4.8) [1]                     | 0                             | 6 (31.6) [9]                                          | 2 (10.5) [2]                  | 12 (24.5)<br>[17]                                                                       | 5 (10.2)<br>[7]               |
| Nasopharyngitis                                       | 2 (8.0) [2]                      | 0                             | 5 (23.8)<br>[7]                 | 0                             | 3 (15.8) [4]                                          | 0                             | 11 (22.4)<br>[21]                                                                       | 0                             |
| Influenza                                             | 3 (12.0)<br>[3]                  | 0                             | 2 (9.5) [2]                     | 0                             | 5 (26.3) [8]                                          | 0                             | 10 (20.4)<br>[13]                                                                       | 0                             |
| Gastroenteritis                                       | 3 (12.0)<br>[3]                  | 0                             | 5 (23.8)<br>[8]                 | 2 (9.5) [2]                   | 0                                                     | 0                             | 7 (14.3)<br>[12]                                                                        | 4 (8.2) [4]                   |
| Respiratory tract<br>infection viral                  | 2 (8.0) [3]                      | 0                             | 1 (4.8) [2]                     | 0                             | 5 (26.3) [14]                                         | 0                             | 7 (14.3)<br>[20]                                                                        | 0                             |
| Urinary tract infection                               | 1 (4.0) [2]                      | 0                             | 1 (4.8) [1]                     | 0                             | 3 (15.8) [4]                                          | 0                             | 7 (14.3)<br>[8]                                                                         | 0                             |

| System Organ Class<br>Preferred Term          | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                               |
|-----------------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|
|                                               | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                               |
|                                               | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                               |
|                                               | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                                                                           | Grade 3<br>and 4 <sup>a</sup> |
| Viral upper<br>respiratory tract<br>infection | 4 (16.0)<br>[5]                  | 0                             | 1 (4.8) [1]                     | 0                             | 4 (21.1) [4]                                          | 0                             | 7 (14.3)<br>[7]                                                                         | 0                             |
| Gastrointestinal viral<br>infection           | 0                                | 0                             | 0                               | 0                             | 3 (15.8) [4]                                          | 0                             | 4 (8.2) [5]                                                                             | 0                             |
| Sinusitis                                     | 2 (8.0) [2]                      | 0                             | 1 (4.8) [1]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 4 (8.2) [4]                                                                             | 0                             |
| Viral infection                               | 4 (16.0)<br>[5]                  | 0                             | 0                               | 0                             | 2 (10.5) [2]                                          | 0                             | 4 (8.2) [4]                                                                             | 0                             |
| <b>Metabolism and<br/>nutrition disorders</b> | 6 (24.0)<br>[13]                 | 0                             | 11 (52.4)<br>[29]               | 1 (4.8) [1]                   | 12 (63.2)<br>[57]                                     | 3 (15.8) [3]                  | 31 (63.3)<br>[165]                                                                      | 9 (18.4)<br>[15]              |
| Hypertriglyceridaemia                         | 1 (4.0) [1]                      | 0                             | 3 (14.3)<br>[7]                 | 0                             | 6 (31.6) [13]                                         | 2 (10.5) [2]                  | 16 (32.7)<br>[40]                                                                       | 3 (6.1) [5]                   |
| Hypoglycaemia                                 | 4 (16.0)<br>[9]                  | 0                             | 4 (19.0)<br>[8]                 | 0                             | 5 (26.3) [27]                                         | 0                             | 14 (28.6)<br>[75]                                                                       | 2 (4.1) [2]                   |
| Hyperglycaemia                                | 0                                | 0                             | 3 (14.3)<br>[5]                 | 0                             | 4 (21.1) [5]                                          | 0                             | 11 (22.4)<br>[20]                                                                       | 0                             |
| Hyperuricaemia                                | 1 (4.0) [1]                      | 0                             | 2 (9.5) [2]                     | 0                             | 4 (21.1) [4]                                          | 0                             | 6 (12.2)<br>[6]                                                                         | 0                             |
| Lactic acidosis                               | 0                                | 0                             | 1 (4.8) [1]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 6 (12.2)<br>[9]                                                                         | 4 (8.2) [4]                   |
| Decreased appetite                            | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 0                             | 3 (15.8) [3]                                          | 0                             | 5 (10.2)<br>[5]                                                                         | 0                             |
| Hyperlactacidaemia                            | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 1 (4.8) [1]                   | 3 (15.8) [4]                                          | 0                             | 4 (8.2) [5]                                                                             | 1 (2.0) [1]                   |
| Hypokalaemia                                  | 0                                | 0                             | 2 (9.5) [4]                     | 0                             | 0                                                     | 0                             | 3 (6.1) [5]                                                                             | 0                             |
| <b>Gastrointestinal<br/>disorders</b>         | 6 (24.0)<br>[21]                 | 2 (8.0) [3]                   | 13 (61.9)<br>[28]               | 1 (4.8) [1]                   | 8 (42.1) [21]                                         | 0                             | 28 (57.1)<br>[89]                                                                       | 1 (2.0) [1]                   |

| System Organ Class<br>Preferred Term                  | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                               |
|-------------------------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|
|                                                       | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                               |
|                                                       | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                               |
|                                                       | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                                                                           | Grade 3<br>and 4 <sup>a</sup> |
| Nausea                                                | 4 (16.0)<br>[10]                 | 1 (4.0) [2]                   | 8 (38.1)<br>[12]                | 1 (4.8) [1]                   | 3 (15.8) [9]                                          | 0                             | 14 (28.6)<br>[28]                                                                       | 1 (2.0) [1]                   |
| Diarrhoea                                             | 2 (8.0) [2]                      | 0                             | 2 (9.5) [2]                     | 0                             | 3 (15.8) [4]                                          | 0                             | 10 (20.4)<br>[15]                                                                       | 0                             |
| Vomiting                                              | 2 (8.0) [2]                      | 0                             | 2 (9.5) [3]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 9 (18.4)<br>[14]                                                                        | 0                             |
| Constipation                                          | 0                                | 0                             | 4 (19.0)<br>[5]                 | 0                             | 2 (10.5) [2]                                          | 0                             | 9 (18.4)<br>[11]                                                                        | 0                             |
| Abdominal pain                                        | 2 (8.0) [5]                      | 0                             | 3 (14.3)<br>[3]                 | 0                             | 2 (10.5) [2]                                          | 0                             | 7 (14.3)<br>[8]                                                                         | 0                             |
| Abdominal pain<br>upper                               | 1 (4.0) [2]                      | 0                             | 1 (4.8) [1]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 6 (12.2)<br>[7]                                                                         | 0                             |
| Dyspepsia                                             | 0                                | 0                             | 2 (9.5) [2]                     | 0                             | 2 (10.5) [2]                                          | 0                             | 6 (12.2)<br>[6]                                                                         | 0                             |
| Musculoskeletal and<br>connective tissue<br>disorders | 2 (8.0) [3]                      | 1 (4.0) [1]                   | 6 (28.6)<br>[6]                 | 0                             | 5 (26.3) [6]                                          | 1 (5.3) [1]                   | 18 (36.7)<br>[22]                                                                       | 1 (2.0) [1]                   |
| Arthralgia                                            | 1 (4.0) [1]                      | 0                             | 2 (9.5) [2]                     | 0                             | 2 (10.5) [2]                                          | 0                             | 7 (14.3)<br>[7]                                                                         | 0                             |
| Muscle spasms                                         | 1 (4.0) [2]                      | 0                             | 3 (14.3)<br>[3]                 | 0                             | 0                                                     | 0                             | 6 (12.2)<br>[6]                                                                         | 0                             |
| Back pain                                             | 0                                | 0                             | 1 (4.8) [1]                     | 0                             | 0                                                     | 0                             | 4 (8.2) [4]                                                                             | 0                             |
| Myalgia                                               | 0                                | 0                             | 0                               | 0                             | 3 (15.8) [4]                                          | 1 (5.3) [1]                   | 4 (8.2) [5]                                                                             | 1 (2.0) [1]                   |
| Nervous system<br>disorders                           | 3 (12.0)<br>[9]                  | 2 (8.0) [3]                   | 5 (23.8)<br>[11]                | 0                             | 5 (26.3) [6]                                          | 1 (5.3) [1]                   | 17 (34.7)<br>[33]                                                                       | 3 (6.1) [3]                   |

| System Organ Class<br>Preferred Term                                | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                               |
|---------------------------------------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|
|                                                                     | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                               |
|                                                                     | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                               |
|                                                                     | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                                                                           | Grade 3<br>and 4 <sup>a</sup> |
| Headache                                                            | 3 (12.0)<br>[9]                  | 0                             | 5 (23.8)<br>[11]                | 0                             | 5 (26.3) [6]                                          | 0                             | 17 (34.7)<br>[33]                                                                       | 0                             |
| <b>General disorders and<br/>administration site<br/>conditions</b> | 6 (24.0)<br>[9]                  | 1 (4.0) [1]                   | 6 (28.6)<br>[12]                | 1 (4.8) [1]                   | 5 (26.3) [5]                                          | 0                             | 15 (30.6)<br>[28]                                                                       | 1 (2.0) [1]                   |
| Fatigue                                                             | 3 (12.0)<br>[6]                  | 1 (4.0) [1]                   | 2 (9.5) [5]                     | 1 (4.8) [1]                   | 2 (10.5) [2]                                          | 0                             | 8 (16.3)<br>[14]                                                                        | 1 (2.0) [1]                   |
| Pyrexia                                                             | 1 (4.0) [1]                      | 0                             | 3 (14.3)<br>[4]                 | 0                             | 0                                                     | 0                             | 5 (10.2)<br>[8]                                                                         | 0                             |
| Malaise                                                             | 2 (8.0) [2]                      | 0                             | 1 (4.8) [3]                     | 0                             | 3 (15.8) [3]                                          | 0                             | 4 (8.2) [6]                                                                             | 0                             |
| <b>Skin and subcutaneous<br/>tissue disorders</b>                   | 0                                | 0                             | 5 (23.8)<br>[5]                 | 0                             | 5 (26.3) [6]                                          | 0                             | 16 (32.7)<br>[19]                                                                       | 0                             |
| Acne                                                                | 0                                | 0                             | 4 (19.0)<br>[4]                 | 0                             | 1 (5.3) [1]                                           | 0                             | 7 (14.3)<br>[7]                                                                         | 0                             |
| Alopecia                                                            | 0                                | 0                             | 0                               | 0                             | 3 (15.8) [3]                                          | 0                             | 6 (12.2)<br>[7]                                                                         | 0                             |
| Rash                                                                | 0                                | 0                             | 1 (4.8) [1]                     | 0                             | 2 (10.5) [2]                                          | 0                             | 5 (10.2)<br>[5]                                                                         | 0                             |
| <b>Blood and lymphatic<br/>system disorders</b>                     | 1 (4.0) [1]                      | 0                             | 3 (14.3)<br>[3]                 | 0                             | 6 (31.6) [10]                                         | 0                             | 15 (30.6)<br>[22]                                                                       | 1 (2.0) [1]                   |
| Anaemia                                                             | 1 (4.0) [1]                      | 0                             | 3 (14.3)<br>[3]                 | 0                             | 3 (15.8) [3]                                          | 0                             | 9 (18.4)<br>[12]                                                                        | 1 (2.0) [1]                   |
| Increased tendency<br>to bruise                                     | 0                                | 0                             | 0                               | 0                             | 4 (21.1) [6]                                          | 0                             | 4 (8.2) [6]                                                                             | 0                             |
| Iron deficiency<br>anaemia                                          | 0                                | 0                             | 0                               | 0                             | 1 (5.3) [1]                                           | 0                             | 4 (8.2) [4]                                                                             | 0                             |

| System Organ Class<br>Preferred Term            | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                               |
|-------------------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|
|                                                 | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                               |
|                                                 | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                               |
|                                                 | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                                                                           | Grade 3<br>and 4 <sup>a</sup> |
| Psychiatric disorders                           | 4 (16.0)<br>[4]                  | 1 (4.0) [1]                   | 4 (19.0)<br>[6]                 | 1 (4.8) [2]                   | 6 (31.6) [10]                                         | 0                             | 14 (28.6)<br>[22]                                                                       | 1 (2.0) [2]                   |
| Anxiety                                         | 2 (8.0) [2]                      | 1 (4.0) [1]                   | 2 (9.5) [2]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 7 (14.3)<br>[7]                                                                         | 0                             |
| Insomnia                                        | 0                                | 0                             | 2 (9.5) [2]                     | 0                             | 4 (21.1) [4]                                          | 0                             | 8 (16.3)<br>[8]                                                                         | 0                             |
| Affect lability                                 | 2 (8.0) [2]                      | 0                             | 1 (4.8) [2]                     | 0                             | 4 (21.1) [5]                                          | 0                             | 5 (10.2)<br>[7]                                                                         | 0                             |
| Renal and urinary disorders                     | 3 (12.0)<br>[3]                  | 0                             | 1 (4.8) [1]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 9 (18.4)<br>[16]                                                                        | 1 (2.0) [1]                   |
| Nephrolithiasis                                 | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 4 (8.2) [9]                                                                             | 0                             |
| Proteinuria                                     | 2 (8.0) [2]                      | 0                             | 0                               | 0                             | 0                                                     | 0                             | 6 (12.2)<br>[7]                                                                         | 0                             |
| Respiratory, thoracic and mediastinal disorders | 2 (8.0) [2]                      | 0                             | 1 (4.8) [1]                     | 0                             | 3 (15.8) [3]                                          | 0                             | 8 (16.3)<br>[9]                                                                         | 0                             |
| Cough                                           | 1 (4.0) [1]                      | 0                             | 0                               | 0                             | 2 (10.5) [2]                                          | 0                             | 4 (8.2) [4]                                                                             | 0                             |
| Oropharyngeal pain                              | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 0                             | 1 (5.3) [1]                                           | 0                             | 5 (10.2)<br>[5]                                                                         | 0                             |
| Endocrine disorders                             | 0                                | 0                             | 5 (23.8)<br>[9]                 | 2 (9.5) [2]                   | 2 (10.5) [2]                                          | 0                             | 8 (16.3)<br>[12]                                                                        | 2 (4.1) [2]                   |
| Adrenal insufficiency                           | 0                                | 0                             | 4 (19.0)<br>[6]                 | 2 (9.5) [2]                   | 0                                                     | 0                             | 5 (10.2)<br>[7]                                                                         | 2 (4.1) [2]                   |
| Cushingoid                                      | 0                                | 0                             | 3 (14.3)<br>[3]                 | 0                             | 2 (10.5) [2]                                          | 0                             | 5 (10.2)<br>[5]                                                                         | 0                             |

| System Organ Class<br>Preferred Term | DTX401-CL301                     |                               |                                 |                               |                                                       |                               | DTX401<br>Registrational Dose:<br>1.0 x 10 <sup>13</sup> GC/kg<br>(N = 49)<br>n (%) [E] |                               |
|--------------------------------------|----------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------|-------------------------------|
|                                      | PEAP                             |                               |                                 |                               | Crossover Period +<br>Follow-up Period                |                               |                                                                                         |                               |
|                                      | Placebo<br>(N = 25)<br>n (%) [E] |                               | DTX401<br>(N = 21)<br>n (%) [E] |                               | Crossover Placebo→<br>DTX401<br>(N = 19)<br>n (%) [E] |                               |                                                                                         |                               |
|                                      | All<br>Grades                    | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                   | Grade 3<br>and 4 <sup>a</sup> | All Grades                                            | Grade 3<br>and 4 <sup>a</sup> | All<br>Grades                                                                           | Grade 3<br>and 4 <sup>a</sup> |
| Hepatobiliary disorders              | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 0                             | 4 (21.1) [4]                                          | 0                             | 8 (16.3)<br>[8]                                                                         | 0                             |
| Hepatomegaly                         | 1 (4.0) [1]                      | 0                             | 1 (4.8) [1]                     | 0                             | 4 (21.1) [4]                                          | 0                             | 8 (16.3)<br>[8]                                                                         | 0                             |
| Vascular disorders                   | 0                                | 0                             | 1 (4.8) [1]                     | 0                             | 0                                                     | 0                             | 3 (6.1) [3]                                                                             | 0                             |
| Hypertension                         | 0                                | 0                             | 1 (4.8) [1]                     | 0                             | 0                                                     | 0                             | 3 (6.1) [3]                                                                             | 0                             |

See Section [8.2.1](#) for description of the treatment groups presented.

For the “Grade 3 and 4” columns, SOC rows represent all subjects and events [E] data, while for the “All grades” columns, SOC rows represent events occurring in ≥4 subjects.

<sup>a</sup> All events reported were Grade 3 except for 1 subject who experienced 1 serious TEAE of multiple organ dysfunction syndrome of life-threatening (Grade 4) severity, and 1 subject who experienced 3 TEAEs (continuum of a single event) of hypertriglyceridemia of life-threatening (Grade 4) severity; during Study 401GSDIA02 for both.

COVID-19, coronavirus disease 2019; GC, genome copies; GGT, gamma-glutamyl transferase; ISS, Integrated Summary of Safety; PEAP, Primary Efficacy Analysis Period; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Source: ISS Tables 14.3.1.3, 14.3.1.7

**Table 37: Applicant – Adverse Drug Reactions Following Treatment with DTX401 (Safety Analysis Set)**

| <b>Adverse Reactions</b>               | <b>DTX401<br/>N = 52<br/>n (%)</b> |
|----------------------------------------|------------------------------------|
| Transaminases increased <sup>a</sup>   | 44 (84.6)                          |
| Nausea                                 | 15 (28.8)                          |
| Infusion-related reaction <sup>b</sup> | 2 (3.8)                            |

<sup>a</sup> Includes Preferred Terms of transaminases increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasemia, and liver function test increased.

<sup>b</sup> Infusion-related reactions, including hypersensitivity are included. Infusion-related reactions include events with features of hypersensitivity with onset during the infusion or up to 6 hours after end of infusion.

At each level of subject summarization, a subject is counted once if the subject reported 1 or more events. n represents the number of subjects at each level of summarization.

Adverse Events were coded using MedDRA, Version 24.1.

MedDRA, Medical Dictionary for Regulatory Activities; ISS, Integrated Summary of Safety

Source: ISS Table 14.3.1.14.2

#### The FDA's Assessment of TEAEs:

Applicant's Table 36 and Table 37 presented all treatment-emergent adverse events (TEAEs) in the safety analysis dataset (N = 58), organized by Preferred Term and pooled across the Phase 3 and Phase 1/2 studies. FDA identified inconsistencies in the Applicant's adverse event summaries (e.g., adrenal insufficiency) and corrected counts are reflected in the FDA-generated tables below. Additionally, grouping of clinically related events results in numerical differences between the Applicant's and FDA-adapted tables.

FDA presents the TEAE of Phase 3 Study DTX401-CL301 (N=46) below. The safety findings in Phase 2 study are described in Section [8.1.2](#), and summarized in [8.2.9](#).

During the PEAP (N = 46; Table 38), TEAEs were reported in all 21 subjects (100%) in the DTX401 group, compared to 22 of 25 subjects (88.0%) in the placebo group, with total event counts of 329 and 218, respectively. The higher overall event burden in the DTX401 group, both in subject incidence and total event count, is consistent with the known safety profile of AAV-based gene therapy and reflects a combination of treatment-related effects, procedural events, and disease-related occurrences.

**Table 38: FDA – TEAEs in PEAP**

| Preferred Term                      | DTX401 (N=21) Events n (%)   Subjects n (%) | Placebo (N=25) Events n (%)   Subjects n (%) |
|-------------------------------------|---------------------------------------------|----------------------------------------------|
| <b>Any TEAE</b>                     | 329   21 (100.0%)                           | 218   22 (88.0%)                             |
| Transaminases Increased $\pm$       | 29   15 (71.4%)                             | 6 (2.8%)   3 (12.0%)                         |
| Nausea                              | 12   8 (38.1%)                              | 10 (4.6%)   4 (16.0%)                        |
| Headache                            | 11   5 (23.8%)                              | 9 (4.1%)   3 (12.0%)                         |
| Hypertriglyceridaemia               | 10   6 (28.6%)                              | 2   2 (8.0%)                                 |
| Adrenal Insufficiency               | 7   5 (23.8%)                               | 0   0                                        |
| Gastroenteritis                     | 9   6 (28.6%)                               | 7   7 (28.0%)                                |
| Hypoglycaemia                       | 8   4 (19.0%)                               | 10   5 (20.0%)                               |
| Lactic Acidosis                     | 6   4 (19.0%)                               | 8   5 (20.0%)                                |
| Abdominal Discomfort                | 5   5 (23.8%)                               | 7   3 (12.0%)                                |
| Gamma-Glutamyltransferase Increased | 5   4 (19.0%)                               | 4   3 (12.0%)                                |
| Constipation                        | 5   4 (19.0%)                               | 0   0                                        |
| Hyperglycaemia                      | 5   3 (14.3%)                               | 0   0                                        |
| Acne / Dermatitis Acneiform         | 4   4 (19.0%)                               | 0   0                                        |
| Hyperuricaemia                      | 3   3 (14.3%)                               | 3   3 (12.0%)                                |
| Cushingoid Features                 | 3   3 (14.3%)                               | 0   0                                        |
| Anaphylaxis                         | 2   2 (9.5%)                                | 0   0                                        |
| DRG & Peripheral Nerve Effects      | 2   2 (9.5%)                                | 1 (0.5%)   1 (4.0%)                          |

Source: Clinical reviewer adapted from ISS Tables 14.3.1.3 and 14.3.1.7, and Table 36, by grouping Preferred Terms with similar clinical events

Abbreviations: PEAP, Primary Efficacy Assessment Period; TEAE, treatment-emergent adverse event

Transaminases Increased was the most prominent treatment-emergent finding differentiating the two groups, occurring in 15/21 DTX401 subjects (71.4%; 29 events) compared to 3/25 placebo subjects (12.0%; 6 events), approximately a sixfold difference in subject incidence. This finding is consistent with a well-characterized immune-mediated hepatic response following AAV vector administration.

Anaphylaxis was reported in 2/21 DTX401 subjects (9.5%; 2 events) and in no placebo subjects, representing a clinically important finding consistent with known risks of AAV-based gene therapy administration.

Adrenal Insufficiency, Cushingoid Features, and Hyperglycaemia were each exclusive to the DTX401 group, with no cases in the placebo group. These findings likely reflect the use of concomitant corticosteroids required to mitigate AAV-related hepatic toxicity, which carries the additional risk of HPA axis suppression. This risk is of particular concern in GSD Ia patients, who are already predisposed to impaired cortisol counterregulation during metabolic stress, making corticosteroid-induced adrenal insufficiency potentially dangerous in this population.

The most common adverse reactions in the PEAP (occurring in  $\geq 10$  % of patients) with higher frequency in during PEAP are shown in section 6 of USPI (Table 39).

**Table 39: FDA – Adverse Reactions in Section 6 of USPI**

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

Source: Reviewer

<sup>1</sup> All events were mild to moderate (< 5.0× ULN), with the exception of one severe (Grade 3) asymptomatic event (peak ALT: 253 U/L). ALT/AST elevations peaked between 4 and 12 weeks post xx administration and resolved within 15 weeks [see Warnings and Precautions (5.2)]

<sup>2</sup> All events were mild to moderate (less than 2.5× ULN)

<sup>3</sup> Two SAEs were reported [see Warnings and Precautions (5.3)]

<sup>4</sup> All events were mild to moderate

<sup>5</sup> Two SAEs with onset within minutes of DTX401 administration [see Warnings and Precautions (5.1)]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; USPI, U.S. Prescribing Information

The crossover safety analysis shown in [Table 40](#) captures TEAEs occurring during the crossover period in two treatment groups: subjects who received placebo and then crossed over to DTX401 (Placebo→DTX401; n = 20) and subjects who received DTX401 and then crossed over to placebo (DTX401→Placebo; n = 20). The analysis population included one subject in the Placebo→DTX401 group and three subjects in the DTX401→Placebo group who did not receive crossover treatment but were followed for safety assessment.

**Table 40: FDA – TEAEs, Crossover Safety Analysis**

| Analysis Population                                  | N = 20<br>(n=19 received DTX401)                             | n = 20<br>(n=17 received placebo)                            |
|------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|
|                                                      | Crossover Placebo to<br>DTX401                               | Crossover DTX401 to<br>Placebo                               |
| Preferred Term<br>(component terms in italics below) | Events, n (%) <sup>a</sup> / Subjects,<br>n (%) <sup>b</sup> | Events, n (%) <sup>a</sup> / Subjects,<br>n (%) <sup>b</sup> |
| Transaminases Increased                              | 36 (180.0%) / 14 (70.0%)                                     | 11 (55.0%) / 6 (30.0%)                                       |
| Upper Respiratory Tract Infection                    | 29 (145.0%) / — <sup>c</sup>                                 | 23 (115.0%) / — <sup>c</sup>                                 |
| Respiratory Tract Infection                          | 18 (90.0%) / 10 (50.0%)                                      | 21 (105.0%) / 17 (85.0%)                                     |
| Influenza                                            | 7 (35.0%) / 5 (25.0%)                                        | 1 (5.0%) / 1 (5.0%)                                          |
| COVID-19                                             | 4 (20.0%) / 4 (20.0%)                                        | 1 (5.0%) / 1 (5.0%)                                          |
| Hypoglycemia                                         | 13 (65.0%) / 5 (25.0%)                                       | 26 (130.0%) / 2 (10.0%)                                      |
| Hypertriglyceridemia                                 | 14 (70.0%) / 9 (45.0%)                                       | 5 (25.0%) / 4 (20.0%)                                        |
| Gastroenteritis                                      | 18 (90.0%) / — <sup>c</sup>                                  | 9 (45.0%) / — <sup>c</sup>                                   |
| Gastroenteritis                                      | 11 (55.0%) / 7 (35.0%)                                       | 6 (30.0%) / 6 (30.0%)                                        |
| Gastrointestinal Viral Infection                     | 2 (10.0%) / 2 (10.0%)                                        | 1 (5.0%) / 1 (5.0%)                                          |
| Diarrhea                                             | 5 (25.0%) / 4 (20.0%)                                        | 2 (10.0%) / 2 (10.0%)                                        |
| Gamma-Glutamyl transferase Increased                 | 11 (55.0%) / 7 (35.0%)                                       | 2 (10.0%) / 2 (10.0%)                                        |
| Nausea                                               | 9 (45.0%) / 3 (15.0%)                                        | 2 (10.0%) / 2 (10.0%)                                        |
| Headache                                             | 7 (35.0%) / 6 (30.0%)                                        | 3 (15.0%) / 3 (15.0%)                                        |
| Blood Bicarbonate Decreased                          | 9 (45.0%) / 3 (15.0%)                                        | 0 (0.0%) / 0 (0.0%)                                          |
| Hyperuricemia                                        | 5 (25.0%) / 5 (25.0%)                                        | 2 (10.0%) / 2 (10.0%)                                        |
| Blood Uric Acid Increased   Hyperuricemia            | 5 (25.0%) / 5 (25.0%)                                        | 2 (10.0%) / 2 (10.0%)                                        |

| <b>Analysis Population</b>             | <b>N = 20<br/>(n=19 received DTX401)</b> | <b>n = 20<br/>(n=17 received placebo)</b> |
|----------------------------------------|------------------------------------------|-------------------------------------------|
| Blood Creatine Phosphokinase Increased | 2 (10.0%) / 2 (10.0%)                    | 5 (25.0%) / 4 (20.0%)                     |
| Lactic Acidosis                        | 5 (25.0%) / 4 (20.0%)                    | 2 (10.0%) / 2 (10.0%)                     |
| Abdominal Discomfort                   | 2 (10.0%) / 2 (10.0%)                    | 4 (20.0%) / 4 (20.0%)                     |
| Hepatic Pain                           | 0 (0.0%) / 0 (0.0%)                      | 5 (25.0%) / 2 (10.0%)                     |
| Weight Decreased                       | 3 (15.0%) / 3 (15.0%)                    | 2 (10.0%) / 2 (10.0%)                     |
| Affect Lability                        | 5 (25.0%) / 4 (20.0%)                    | 0 (0.0%) / 0 (0.0%)                       |
| Hyperglycemia                          | 5 (25.0%) / 4 (20.0%)                    | 0 (0.0%) / 0 (0.0%)                       |
| Epistaxis                              | 3 (15.0%) / 1 (5.0%)                     | 2 (10.0%) / 1 (5.0%)                      |
| Procedural Pain                        | 4 (20.0%) / 4 (20.0%)                    | 1 (5.0%) / 1 (5.0%)                       |
| Anemia                                 | 2 (10.0%) / 2 (10.0%)                    | 2 (10.0%) / 2 (10.0%)                     |
| Anxiety                                | 2 (10.0%) / 2 (10.0%)                    | 2 (10.0%) / 2 (10.0%)                     |
| Alopecia                               | 3 (15.0%) / 3 (15.0%)                    | 1 (5.0%) / 1 (5.0%)                       |
| Appetite Disorder                      | 4 (20.0%) / 4 (20.0%)                    | 0 (0.0%) / 0 (0.0%)                       |
| Urinary Tract Infection                | 3 (15.0%) / 3 (15.0%)                    | 1 (5.0%) / 1 (5.0%)                       |
| Procedural Nausea                      | 3 (15.0%) / 3 (15.0%)                    | 1 (5.0%) / 1 (5.0%)                       |
| Ultrasound Liver Abnormal              | 3 (15.0%) / 3 (15.0%)                    | 0 (0.0%) / 0 (0.0%)                       |

Source: Clinical review team

<sup>a</sup> Percentage based on total number of events relative to total events in the group.

<sup>b</sup> Percentage based on total number of subjects with ≥1 event in the group (N = 20 per group).

<sup>c</sup> Subject count not summed across component terms due to potential overlap within the same subject.

Abbreviations: DTX401, adeno-associated virus serotype 2 (AAV2) vector encoding human G6PC; PEAP, Primary Efficacy Assessment Period

During CO, hepatic reactions (transaminases, GGT, hepatic pain) show a consistent pattern: transaminase and GGT elevations are concentrated in subjects receiving DTX401 for the first time during crossover, while hepatic pain clusters in those who received DTX401 earlier. This pattern is consistent with an immune-mediated or inflammatory hepatic response associated with AAV vector administration.

Metabolic events (hypoglycemia, hypertriglyceridemia, hyperglycemia) show complex patterns that may reflect the therapeutic effect of G6PC restoration at different disease stages.

Most TEAEs appear manageable in both groups, with no single category dominating at the population level in a way that would suggest a new or unexpected safety concern beyond those already characterized during the PEAP.

## Adverse Events of Special Interest

### *Anaphylactic and Infusion-Related Reactions (FDA SAE Table 34)*

Two Anaphylactic/IRRs occurring during PEAP within 1 to 6 minutes of administration, each resulting in immediate discontinuation of the infusion. Symptoms included chest pain, vomiting, tachycardia, and urticarial rash in one subject, and coughing, difficulty breathing, decreased oxygen saturation, and reticular rash in the other. Hypotension was not reported and epinephrine was not administered; both events resolved with treatment.

### *Hepatic Toxicity*

In the Phase 3 study (N=40), 80% of DTX401-treated subjects experienced at least one hepatic reaction TEAE. Events were predominantly nonserious, Grade 1–2, transient, and asymptomatic, managed with corticosteroids. ALT/AST elevations peaked at 4–12 weeks post-administration and resolved in 92% of subjects; 6 subjects (8%) had unresolved, nonserious elevations at cutoff (5 Grade 1, 1 Grade 2).

Grade 3 ALT elevations occurred in 1 subject (6.7%) in the PEAP DTX401 group and 2 subjects in the Crossover Placebo→DTX401 group. No Grade 3 AST or Grade 4 ALT/AST elevations were observed, and no subjects met Hy's Law criteria. Notably, ALT/AST elevations are also commonly associated with underlying GSDIa independent of AAV gene therapy.

### *Adrenal Insufficiency*

Across the Phase 3 (DTX401-CL301, N=46) and Phase 1/2 (N=12) studies, adrenal insufficiency TEAEs were observed exclusively in DTX401-treated subjects.

During the **PEAP (Weeks 1–48)**, 5 DTX401-treated subjects experienced 7 adrenal insufficiency TEAEs.

- Subject (b) (6) (17F) developed adrenal insufficiency during a prednisolone taper, presenting with hypotension and tachycardia that escalated to ICU admission requiring stress-dose IV hydrocortisone and 7 months of hydrocortisone replacement. Recorded as 3 separate AEs to reflect changes in seriousness and severity over time, this event warrants consideration for reclassification as a life-threatening Grade 4 SAE (Applicant reported as Grade 3) given the level of medical intervention required.
- Subject (b) (6) (16M) developed adrenal insufficiency during a second prednisolone course, complicated by acute gastroenteritis, presenting with tachycardia, tachypnea, pallor, and decreased responsiveness requiring hospitalization and stress-dose IV hydrocortisone. A post-discharge hypoglycemic episode occurred upon non-resumption of prednisolone; the event resolved after a 3-week taper.

The remaining 3 subjects had nonserious, asymptomatic TEAEs identified solely through cortisol/ACTH laboratory findings during prednisolone doses of 20–60 mg/day, characterized by the sponsor as physiologic HPA axis suppression. All resolved without clinical consequence.

During crossover (Weeks 48–96), Subject (b) (6) (21F) experienced 2 additional Grade 2, asymptomatic TEAEs of HPA axis suppression, identified biochemically and resolving without clinical consequence.

In PEAP and crossover, 6 subjects experienced 9 adrenal insufficiency-related TEAEs, of which 2 were clinically significant SAEs requiring acute medical intervention.

### *Metabolic Derangement*

Hypertriglyceridemia and hyperglycemia occurred at notably higher incidences in the DTX401 group compared to placebo during the PEAP (28.6% vs. 8.0% and 14.3% vs. 0%, respectively). Additionally, SAEs reported in the DTX401 group included one case each of hyperlacticacidemia, lactic acidosis, and hypoglycemia, compared to none in the placebo group during the PEAP.

### *AAV Vector Integration and Risk of Tumorigenicity/Malignancy*

There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome. GENGLYCOS is composed of a recombinant, non-replicating AAV8 vector whose DNA persists largely in episomal form. Random integration of recombinant AAV-vector DNA into human DNA has been reported with AAV gene therapies. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity

## **8.2.4.7 Laboratory Findings**

### Data:

Results below focus on clinical laboratory evaluations pertinent to the disease state or gene therapy administration.

**Liver Aminotransferases:** Across Study DTX401-CL301 and Studies 401GSDIA01 and 401GSDIA02, ALT and AST elevations generally peaked between Week 4 and Week 15 for most subjects (ISS Table 14.3.1.14.5; DTX401-CL301 Week 96 CSR Figures 14.3.5.1.8, 14.3.5.1.9; 401GSDIA02 CSR Figures 14.3.5.1.2, 14.3.5.1.3), returning to their Baseline levels or within normal range within the first year following DTX401 administration. No subjects satisfied Hy's Law criteria (DTX401-CL301 Week 96 CSR Listing 16.2.8.8; 401GSDIA02 CSR Listing 16.2.8.6). There were no associated elevations in bilirubin, albumin, or international normalized ratio (INR) (which would be indicative of hepatocyte injury), and no evidence of liver synthetic dysfunction was observed. Hepatic reactions are discussed in more detail in Section [8.2.4.5](#).

**Low-density Lipoprotein Cholesterol (LDL-C):** Across studies, mean LDL-C levels varied slightly across visits, but overall trends remained stable over time (DTX401-CL301 Week 96 CSR Figure 14.3.5.1.10; 401GSDIA02 CSR Figure 14.3.5.1.4). In Study DTX401-CL301, 1 subject in the DTX401 group had a nonserious TEAE of LDL increased, which resolved spontaneously by the end of the PEAP. The event was mild (Grade 1) in severity and assessed as unrelated to DTX401 by the Investigator. One subject in the Crossover Placebo→DTX401 group had a nonserious TEAE of LDL increased, mild (Grade 1) in severity, assessed as unrelated to DTX401 by the Investigator, and reported as ongoing at the time of the report (DTX401-CL301 Week 96 CSR Listing 16.2.7.1.1). In Study 401GSDIA02, 1 subject experienced 1 nonserious TEAE of dyslipidemia, of mild (Grade 1) severity, assessed as not related to DTX401 by the Investigator, and which was resolving at the time of the data cut for the Study 401GSDIA02 CSR (401GSDIA02 Listing 16.2.7.1.1). No additional TEAEs of elevated cholesterol or TEAEs suggestive of clinically significant sequelae due to atherosclerosis

or coronary artery disease associated with elevations in cholesterol were reported.

**Triglycerides:** Across studies, mean triglyceride levels showed an increase from Baseline before plateauing over time (DTX401-CL301 Week 96 CSR Figure 14.3.5.1.6; 401GSDIA02 CSR Figure 14.3.5.1.1). See Section [8.1.4.2.1](#) for additional discussion on triglyceride elevations. Hypertriglyceridemia is discussed in Section [8.2.4.5](#).

**Renal Function:** Across studies, eGFRs remained stable over time or showed mild improvements post-DTX401 treatment across studies. In Study DTX401-CL301, there were no clinically significant changes in urine albumin creatinine ratio (UACR) throughout the study in either treatment group (DTX401-CL301 Week 96 CSR Tables 14.3.5.1.1.3, 14.3.5.1.1.4). In Studies 401GSDIA01 and 401GSDIA02, increases in UACR were observed in Cohorts 1 – 3, while a decrease was observed in Cohort 4 (401GSDIA02 CSR Table 14.3.5.1.1). The number of subjects experiencing a post-baseline grade increase in clinical safety laboratory assessments are presented for Study DTX401-CL301 ([Table 41](#)) and Studies 401GSDIA01 and 401GSDIA02 ([Table](#)).

The Applicant's Position:

Consistent with AAV gene therapy administration, elevations in aminotransferase levels post-DTX401 dosing were observed and were generally mild to moderate and transient (Section [8.2.4.5](#) and Section [8.2.4.6](#)). In addition, triglyceride elevations were observed (Section [8.1.4.2.1](#)). Overall, clinical laboratory evaluations pertinent to the disease state did not show clinically significant trends post-DTX401 administration.

**Table 41: Applicant – Number of Subjects With Post-baseline Grade Increase, for any Clinical Safety Laboratory Assessments Abnormal in ≥ 10% Subjects in Total DTX401: Day 1 + Week 48 (N = 40) Group (Study DTX401-CL301) (Safety Analysis Set)**

|                               | DTX401-CL301     |         |         |                 |         |         |                                     |         |         |                                            |         |         |
|-------------------------------|------------------|---------|---------|-----------------|---------|---------|-------------------------------------|---------|---------|--------------------------------------------|---------|---------|
|                               | PEAP             |         |         |                 |         |         | Crossover Period + Follow-up Period |         |         | PEAP + Crossover Period + Follow-up Period |         |         |
|                               | Placebo (N = 25) |         |         | DTX401 (N = 21) |         |         | Crossover Placebo → DTX401 (N = 19) |         |         | Total DTX401: Day 1 + Week 48 (N = 40)     |         |         |
|                               | All Grades       | Grade 3 | Grade 4 | All Grades      | Grade 3 | Grade 4 | All Grades                          | Grade 3 | Grade 4 | All Grades                                 | Grade 3 | Grade 4 |
| <b>Chemistry</b>              |                  |         |         |                 |         |         |                                     |         |         |                                            |         |         |
| ALT increase                  | 7                | 1       | 0       | 15              | 1       | 0       | 14                                  | 2       | 0       | 30                                         | 4       | 0       |
| Alkaline phosphatase increase | 1                | 0       | 0       | 3               | 0       | 0       | 1                                   | 0       | 0       | 7                                          | 0       | 0       |
| AST increase                  | 6                | 0       | 0       | 13              | 0       | 0       | 12                                  | 0       | 0       | 27                                         | 0       | 0       |
| Bicarbonate decrease          | 8                | 0       | 0       | 10              | 0       | 0       | 14                                  | 0       | 0       | 28                                         | 0       | 0       |
| Calcium increase              | 3                | 0       | 0       | 6               | 0       | 0       | 9                                   | 0       | 0       | 19                                         | 0       | 0       |
| Cholesterol increase          | 8                | 0       | 0       | 13              | 0       | 2       | 14                                  | 1       | 1       | 29                                         | 2       | 3       |
| Creatine kinase increase      | 4                | 0       | 0       | 3               | 1       | 1       | 0                                   | 0       | 0       | 9                                          | 0       | 3       |
| Creatinine increase           | 8                | 1       | 0       | 6               | 0       | 0       | 8                                   | 0       | 0       | 16                                         | 0       | 0       |
| GGT increase                  | 5                | 0       | 0       | 6               | 1       | 0       | 5                                   | 0       | 0       | 16                                         | 1       | 0       |
| Glucose increase              | 1                | 0       | 0       | 5               | 0       | 0       | 8                                   | 0       | 0       | 14                                         | 0       | 0       |
| Glucose decrease              | 7                | 0       | 0       | 5               | 0       | 0       | 14                                  | 1       | 0       | 27                                         | 1       | 0       |
| Magnesium increase            | 2                | 0       | 0       | 3               | 0       | 0       | 4                                   | 0       | 0       | 8                                          | 0       | 0       |
| Potassium increase            | 1                | 0       | 0       | 3               | 0       | 0       | 3                                   | 0       | 0       | 9                                          | 0       | 0       |

|                        | DTX401-CL301     |         |         |                 |         |         |                                     |         |         |                                            |         |         |
|------------------------|------------------|---------|---------|-----------------|---------|---------|-------------------------------------|---------|---------|--------------------------------------------|---------|---------|
|                        | PEAP             |         |         |                 |         |         | Crossover Period + Follow-up Period |         |         | PEAP + Crossover Period + Follow-up Period |         |         |
|                        | Placebo (N = 25) |         |         | DTX401 (N = 21) |         |         | Crossover Placebo → DTX401 (N = 19) |         |         | Total DTX401: Day 1 + Week 48 (N = 40)     |         |         |
|                        | All Grades       | Grade 3 | Grade 4 | All Grades      | Grade 3 | Grade 4 | All Grades                          | Grade 3 | Grade 4 | All Grades                                 | Grade 3 | Grade 4 |
| Potassium decrease     | 2                | 0       | 0       | 3               | 0       | 0       | 5                                   | 1       | 0       | 9                                          | 1       | 0       |
| Sodium decrease        | 2                | 0       | 0       | 4               | 0       | 0       | 6                                   | 0       | 0       | 15                                         | 0       | 0       |
| Triglycerides increase | 12               | 4       | 0       | 16              | 4       | 7       | 17                                  | 5       | 6       | 37                                         | 13      | 14      |
| Urate increase         | 5                | 5       | 0       | 7               | 7       | 0       | 8                                   | 8       | 0       | 18                                         | 18      | 0       |
| eGFR decrease          | 0                | 0       | 0       | 2               | 0       | 0       | 2                                   | 0       | 0       | 4                                          | 0       | 0       |
| <b>Hematology</b>      |                  |         |         |                 |         |         |                                     |         |         |                                            |         |         |
| Lymphocytes Increase   | 4                | 0       | 0       | 1               | 0       | 0       | 6                                   | 0       | 0       | 8                                          | 0       | 0       |

See Section [8.2.1](#) for description of the treatment groups presented.

Laboratory abnormalities included in this table correspond to those observed in ≥ 10% subjects in the Total DTX401: Day 1 + Week 48 (N = 40) group for any of the baseline grade subcategories. Only subjects who experienced at least one grade worsening on study are included, and n included in this table correspond to the sum of the n in the different baseline grade subcategories.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSR, Clinical Study Report; eGFR, glomerular filtration rate, estimated (ml/min/1.73 m<sup>2</sup>); GGT, gamma-glutamyl transferase; PEAP, Primary Efficacy Analysis Period

Source: DTX401-CL301 Week 96 CSR Tables 14.3.5.1.2.1, 14.3.5.1.2.2, 14.3.5.1.2.3, 14.3.5.1.2.4, 14.3.5.2.2.1, 14.3.5.2.2.2

**Table 42: Applicant – Number of Subjects With Post-baseline Grade Increase, for any Clinical Safety Laboratory Assessments Abnormal in ≥ 10% Subjects in the Cohort 1-4 (N = 12) Group (Studies 401GSDIA01 and 401GSDIA02) (Full Analysis Set)**

|                               | 401GSDIA01 and 401GSDIA02 |         |         |                        |         |         |
|-------------------------------|---------------------------|---------|---------|------------------------|---------|---------|
|                               | Cohort 2-4<br>(N = 9)     |         |         | Cohort 1-4<br>(N = 12) |         |         |
|                               | All Grades                | Grade 3 | Grade 4 | All Grades             | Grade 3 | Grade 4 |
| <b>Chemistry</b>              |                           |         |         |                        |         |         |
| ALT increase                  | 9                         | 2       | 2       | 12                     | 2       | 4       |
| Alkaline phosphatase increase | 1                         | 0       | 1       | 3                      | 0       | 3       |
| AST increase                  | 9                         | 1       | 2       | 12                     | 1       | 4       |
| Bicarbonate decrease          | 6                         | 0       | 0       | 9                      | 0       | 0       |
| Bilirubin increase            | 2                         | 0       | 2       | 4                      | 0       | 4       |
| Calcium increase              | 5                         | 0       | 0       | 7                      | 0       | 1       |
| Calcium decrease              | 2                         | 0       | 2       | 5                      | 0       | 4       |
| Cholesterol increase          | 8                         | 1       | 4       | 11                     | 1       | 6       |
| Creatine kinase increase      | 6                         | 0       | 3       | 8                      | 0       | 5       |
| Creatinine increase           | 1                         | 0       | 1       | 2                      | 0       | 2       |
| GGT increase                  | 7                         | 1       | 2       | 9                      | 1       | 3       |
| Glucose decrease              | 9                         | 0       | 0       | 12                     | 0       | 0       |
| Potassium increase            | 2                         | 0       | 0       | 4                      | 0       | 0       |
| Potassium decrease            | 6                         | 0       | 0       | 7                      | 0       | 0       |
| Sodium decrease               | 3                         | 1       | 0       | 5                      | 1       | 0       |
| Triglycerides increase        | 9                         | 3       | 5       | 11                     | 3       | 7       |
| Urate increase                | 5                         | 5       | 0       | 8                      | 8       | 0       |
| <b>Hematology</b>             |                           |         |         |                        |         |         |
| Eosinophils increase          | 2                         | 0       | 0       | 4                      | 0       | 0       |
| Lymphocytes increase          | 5                         | 0       | 0       | 7                      | 0       | 0       |
| Neutrophils decrease          | 2                         | 0       | 0       | 2                      | 0       | 0       |

See Section [8.2.1](#) for description of the treatment groups presented.

Laboratory abnormalities included in this table correspond to those observed in ≥ 10% subjects in the Cohort 1-4 (N = 12) group for any of the baseline grade subcategories. Only subjects who experienced at least one grade worsening on study are included, and n included in this table correspond to the sum of the n in the different baseline grade subcategories.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSR, Clinical Study Report; GGT, gamma-glutamyl transferase

Source: 401GSDIA02 CSR Tables 14.3.5.1.2, 14.3.5.2.2

The FDA's Assessment:

FDA concurs with the Applicant's data presentation in Table 41 and Table 42 and provides additional presentation of clinically relevant laboratory findings, including pre-controlled fasting challenge (CFC) metabolic parameters (e.g., triglycerides, lactic acid, and uric acid).

Assessment of metabolic control served dual purposes in this study: as an efficacy measure to evaluate the degree of metabolic improvement following DTX401 treatment, and as a safety indicator to characterize disease-associated metabolic complications inherent to GSD1a. Specifically, lactate, uric acid, and triglycerides were assessed to examine the degree of metabolic control achieved during the study. Results are based on observational data and are presented in Table 25 (Section [8.1.1](#)).

Across all three parameters, the DTX401-treated group trended toward greater elevations compared to placebo, with the most pronounced difference observed for triglycerides. Although these analyses are observational and should be interpreted with caution, the findings suggest that the expected improvement in metabolic control was not demonstrated in the context of reduced cornstarch intake, further indicating that the degree of enzyme activity restoration achieved with DTX401 was insufficient to translate into meaningful improvement in the metabolic complications associated with GSD1a.

#### **8.2.4.8 Vital Signs**

Data:

No clinically meaningful mean changes from Baseline were observed for vital signs (DTX401-CL301 Week 96 CSR Tables 14.3.6.1.1.1, 14.3.6.1.1.2; 401GSDIA02 CSR Table 14.3.6.1.1). Isolated and transient abnormalities in heart rate, systolic and diastolic blood pressure were noted, none of which were temporally associated with TEAEs (DTX401-CL301 Week 96 CSR Tables 14.3.6.1.2.1, 14.3.6.1.2.2; 401GSDIA02 CSR Table 14.3.6.1.2).

The Applicant's Position:

DTX401 did not appear to have clinically meaningful adverse effects on subject vital signs during any clinical study.

The FDA's Assessment:

FDA concurs.

#### **8.2.4.9 Electrocardiograms (ECGs)**

Data:

No clinically meaningful trends were observed in any ECG parameters after DTX401 treatment (DTX401-CL301 Week 96 CSR Tables 14.3.6.3.1.1, 14.3.6.3.1.2; 401GSDIA02 CSR Listing 16.2.7.2.2).

The Applicant's Position:

DTX401 did not appear to have clinically meaningful adverse effects on subject ECG parameters during any clinical study.

The FDA's Assessment:

FDA concurs.

**8.2.4.10 QT**

Data/Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA concurs.

**8.2.4.11 Immunogenicity**

**Safety Considerations Related to the Immune Response to AAV8**

Data:

In Study DTX401-CL301, 4 subjects who had positive anti-AAV8 antibodies at some point prior to dosing were dosed with DTX401, despite having screened negative. Two subjects were positive on the day of DTX401 administration, with low titer (1:34 and 1:53). The other 2 subjects were positive at 1 or several timepoints during the PEAP, but negative at the time of DTX401 dosing at Week 48. There were no IRRs reported in these 4 subjects and their safety profiles were consistent with study participants who received DTX401 (DTX401-CL301 Week 96 CSR Listing 16.2.7.3.1).

Overall in Studies 401GSDIA01 and 401GSDIA02 and Study DTX401-CL301, all subjects that received DTX401 seroconverted or demonstrated an increase in anti-AAV8 antibody titer at the 4 weeks post-dose, with high (millions) anti-AAV8 antibody titers present, as expected. Titers remained positive at the last collection (DTX401-CL301 Week 96 CSR Tables 14.3.7.1.1.1.1, 14.3.7.1.1.1.2, 14.3.7.1.1, 14.3.7.1.2).

The Applicant's Position:

The development of anti-AAV8 antibodies post-DTX401 administration had no apparent impact on the safety of subjects treated with DTX401. The safety in the 4 participants with anti-AAV8 antibodies prior to DTX401 administration (including the 2 participants with low titer anti-AAV8 antibodies at the time of dosing) were consistent with the overall DTX401-treated group.

**Safety Considerations Related to the Immune Response to G6Pase**

Data:

In Study DTX401-CL301, all subjects were negative for anti-G6Pase antibodies at Baseline. During the study, 11 of 40 subjects treated with DTX401 demonstrated an increase in anti-G6Pase antibodies. Anti-G6Pase antibody titers were low with the highest observed titer of 1:40 (DTX401-CL301 Week 96 CSR Tables 14.3.7.2.1, 14.3.7.2.2, 14.3.7.2.1.1.1). Anti-G6Pase antibody titers of 1:40 or less are not expected

to impact clinical outcomes.

In Studies 401GSDIA01 and 401GSDIA02, all subjects were negative for anti-G6Pase antibodies at Baseline. Except for a single subject at a single timepoint only, all subsequent assessments were negative for the presence of anti-G6Pase antibodies (401GSDIA02 CSR Table 14.3.7.3).

The Applicant's Position:

There was no apparent impact of anti-G6Pase antibodies on the safety of DTX401. The clinical significance of anti-G6Pase antibodies is not known.

The FDA's Assessment:

Refer to Section [6](#).

#### **8.2.4.12 Analysis of Submission-Specific Safety Issues**

Data/Applicant's Position:

There are no safety issues specific to this application. Not applicable.

The FDA's Assessment:

Not applicable.

#### **Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

Data/Applicant's Position:

No COA analyses informing safety/tolerability were performed. Not applicable.

The FDA's Assessment:

Not applicable.

#### **Safety Analyses by Demographic Subgroups**

Data:

##### **Age**

All enrolled subjects in Studies 401GSDIA01 and 401GSDIA02 were adults (401GSDIA02 CSR Listing 16.2.4.1).

In Study DTX401-CL301, in the DTX401 group during the PEAP, severe (Grade 3) TEAEs and serious TEAEs were reported more frequently in pediatric subjects compared to adult subjects, including DTX401-related severe (Grade 3) and serious DTX401-related TEAEs as assessed by the Investigator. Similarly, in the Crossover Placebo→DTX401 group, serious TEAEs were reported more frequently in pediatric subjects compared to adult subjects (DTX401-CL301 Week 96 CSR Tables 14.3.1.1.3.3, 14.3.1.1.3.4).

In Study DTX401-CL301, in the Total DTX401 (Day 1 + Week 48) group (pediatric, N = 15; adult, N = 25), a higher percentage of pediatric subjects than adult subjects

reported TEAEs related to study participation (11 [73.3%] and 9 [36.0%], respectively). DTX401-related and prednisolone-related TEAEs were reported at a similar frequency in pediatric and adult subjects. The most frequently reported serious TEAEs in both groups were gastroenteritis and associated events (PTs: gastroenteritis viral, gastroenteritis, gastritis viral) (DTX401-CL301 Week 96 CSR Tables 14.3.1.1.3.5, 14.3.1.1.3.6, Listing 16.2.7.1.1).

A higher proportion of pediatric subjects experienced serious TEAEs (12 pediatric subjects [80.0%] and 9 adult subjects [36.0%]), including serious related TEAEs. The serious DTX401-related TEAEs reported in pediatric subjects included 2 events of IRRs (PT: anaphylactic reaction; led to discontinuation of study drug), 1 event of hypertriglyceridemia (also related to study participation) and 1 event of hyperlactacidemia (also related to prednisolone). The serious prednisolone-related TEAEs reported in pediatric subjects included 2 events of adrenal insufficiency. The 2 serious DTX401-related TEAEs of IRRs during the PEAP were reported in younger (8–12 years; N = 9) pediatric subjects; the 2 serious prednisolone-related TEAEs of adrenal insufficiency during the PEAP were reported in older (13–17 years; N = 11) pediatric subjects. The serious study participation-related TEAEs reported in pediatric subjects included 2 events of hypertriglyceridemia and 1 event of transaminases increased. Only 1 serious related TEAE was reported in 1 adult subject (PT: lactic acidosis, assessed as related to prednisolone) (DTX401-CL301 Week 96 CSR Tables 14.3.1.1.3.5, 14.3.1.1.3.6, Listing 16.2.7.1.1).

Overall, severe (Grade 3) TEAEs were reported more frequently in pediatric subjects (11 pediatric subjects [73.3%] and 14 adult subjects [56.0%]), including severe (Grade 3) DTX401-related TEAEs (PTs in pediatric subjects: anaphylactic reaction [2 events], ALT increased, hypertriglyceridemia, transaminases increased, and hyperlactacidemia [each 1 event]; PTs in adult subjects: transaminases increased [2 events], and ALT increased [1 event]). Of the severe (Grade 3) events of aminotransferase elevations based on CTCAE criteria and considered related to DTX401 by the Investigator, none were reported in pediatric subjects. Three serious TEAEs of hypertriglyceridemia were reported, all in pediatric subjects, including 1 event assessed as related by the Investigator to both DTX401 and study participation (DTX401-CL301 Week 96 CSR Tables 14.3.1.1.3.5, 14.3.1.1.3.6, Listing 16.2.7.1.1).

### **Gender**

Overall, the TEAE profile was consistent across genders (male, N = 31; female, N = 29) (ISS Tables 14.3.1.1.2.1, 14.3.1.1.2.2).

### **BMI**

Overall, the TEAE profile was consistent across BMI categories (underweight [< 5th percentile for pediatrics, BMI < 18.5 for adults], no subjects were part of this category; normal weight [5-85th percentile for pediatrics, BMI 18.5-24 for adults], N = 14; overweight [85-95th percentile for pediatrics, BMI 25-29 for adults], N = 21; and obese [95th or greater for pediatrics, BMI 30+ for adults], N = 17) (ISS Tables 14.3.1.1.3.1, 14.3.1.1.3.2, 14.3.1.1.3.3, 14.3.1.1.3.4).

The Applicant's Position:

A higher percentage of pediatric vs adult subjects reported TEAEs related to study participation, serious TEAEs, and severe (Grade 3) TEAEs. Overall, DTX401 demonstrated an acceptable and manageable safety profile in pediatric subjects, and no dose adjustments is warranted for pediatric patients aged 8 to 17 years. The TEAE profile was consistent across the gender and BMI subgroups.

The FDA's Assessment:

The FDA agrees that the pediatric population <18 years suffered a greater burden of treatment emergent adverse events serious adverse events than the adult population (80% versus 36%).

### **8.2.5 Safety Results: Phase 1/2**

### **8.2.6 Specific Safety Studies/Clinical Trials**

Data/Applicant's Position:

Not applicable.

The FDA's Assessment:

Refer to Section [8.1.2](#).

### **8.2.7 Additional Safety Explorations**

#### **8.2.7.1 Human Carcinogenicity or Tumor Development**

Data:

For DTX401, human carcinogenicity or tumor development studies were not conducted. Based on known class effects of AAV gene therapies, insertional mutagenesis and malignancy is considered an important potential risk for DTX401. The Sponsor utilized a comprehensive MedDRA search strategy (Malignancies SMQ; broad and narrow terms) to identify potential events of malignancy. One nonserious, mild (Grade 1) event of basal cell carcinoma (BCC) was identified in 1 subject enrolled in Study 401GSDIA02. The event occurred >4.5 years after DTX401 administration and resolved (401GSDIA02 CSR Table 14.3.1.7.3.1, Listing 16.2.7.1.1; 401GSDIA01 CSR Listing 16.2.4.2).

The Applicant's Position:

The event of BCC was assessed as not related to DTX401 by the Investigator and Sponsor and there have been no events suggestive of AAV-related malignancy.

The FDA's Assessment:

FDA concurs.

#### **8.2.7.2 Human Reproduction and Pregnancy**

Data:

Female subjects of childbearing potential who had a positive pregnancy test, were unwilling to use contraception, or were breastfeeding were excluded from the DTX401

clinical trials. The additional completed nonclinical studies including a vector shedding study (in mice), a reproductive and developmental toxicity study (in mice), a germline transmission study (in mice) and a 6-month toxicity study (in monkeys) show no evidence of germline transmission. Additional details are provided in Section

The Applicant's Position:

The proposed product labeling states that DTX401 should not be used during pregnancy. Routine risk-minimization measures have been incorporated into the labeling to advise females of reproductive potential to use effective contraception for at least 48 weeks following administration of DTX401. In addition, the labeling indicates that decisions regarding breastfeeding should consider the developmental and health benefits of breastfeeding alongside the mother's clinical need for DTX401 and any potential adverse effects on the breastfed infant from DTX401 or from the underlying maternal condition. Male patients and/or their female partners must avoid pregnancy by using an effective form of contraception and male patients must not donate semen for 6 months post infusion.

The FDA's Assessment:

Refer to FDA Pharmacology-Toxicology Review for details.

### **8.2.7.3 Pediatrics and Assessment of Effects on Growth**

Data:

In Study DTX401-CL301 following DTX401 treatment, the proportion of subjects whose physical examination was abnormal and clinically significant was mostly consistent with Baseline. There were no TEAEs of growth delays in any DTX401 study. No trends were observed in differences in Tanner stage over time nor between treatment groups (DTX401-CL301 Week 96 CSR Tables 14.3.6.4.1.1, 14.3.6.4.1.2, 14.3.6.5.1.1, 14.3.6.5.1.2).

The Applicant's Position:

No clinically meaningful changes in physical examinations were observed following DTX401 treatment.

The FDA's Assessment:

FDA reviewed the referenced tables in the BLA submission and concurs with the Applicant's position.

### **8.2.7.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Data:

Overdose, drug abuse potential, and withdrawal and rebound have not been evaluated. DTX401 is a gene therapy product delivering a transgene expressing the G6Pase protein, a mechanism of action that is not associated with any known mechanism for the development of substance dependence or abuse.

The available data on long-term durability of efficacy are summarized in Section [8.1.4.3](#)

and are consistent with continuing durability of efficacy and not indicative of withdrawal or rebound effects.

The Applicant's Position:

DTX401 is a gene therapy product that is individually prescribed and prepared by a pharmacist upon confirmation of the subject's body weight, and administered as a one-time, single dose under the direct supervision of a qualified healthcare provider. Under these conditions, the risk of overdose or drug abuse is low.

The FDA's Assessment:

Not applicable.

## **8.2.8 Safety in the Postmarket Setting**

### **8.2.8.1 Safety Concerns Identified Through Postmarket Experience**

Data/Applicant's Position:

DTX401 has not been approved and marketed in any region.

The FDA's Assessment:

FDA concurs.

### **8.2.8.2 Expectations on Safety in the Postmarket Setting**

The Applicant's Position:

Safety in the postmarket setting is expected to be generally similar to that observed in the DTX401 clinical trial program. Overall, the risk-mitigation strategies incorporated in the Study DTX401-CL301 protocol were effective, and these measures have been integrated into the proposed product labeling. The label will include instructions for the management of DTX401-related risks and informing patients of these risks. Furthermore, DTX401 will be subject to restricted medical prescription and administration will occur at qualified medical sites. Postmarket safety monitoring of DTX401 includes routine and additional pharmacovigilance activities. Long-term safety and efficacy will be further characterized via the ongoing GSDIa DMP; the Sponsor will conduct risk assessment on an ongoing basis, both through continued long-term evaluation of clinical trial participants and commercially treated patients for at least 10 years post DTX401 administration.

The FDA's Assessment:

FDA concurs that the safety profile in the postmarket setting is expected to be generally similar to that observed in the DTX401 clinical trial program. For a summary of warnings, precautions, and safety findings, please refer to USPI sections 5 and 6. The Applicant has committed to conducting a longitudinal, observational study (PMC) to evaluate the long-term safety of GENGLYCOS.

## **8.2.9 Integrated Assessment of Safety**

Data:

- In the DTX401 Registrational Dose group, the median duration of follow-up was 2.1 (range: 1.0 to 5.5) years (Section [8.2.2.1](#)).
- No deaths and no TEAEs leading to study discontinuation have been reported in any subject treated with DTX401 (Section [8.2.4.1](#), Section [8.2.4.3](#)).
- Three (continuum of the same event in 1 subject) life-threatening (Grade 4) TEAEs of hypertriglyceridemia were considered related to DTX401 by the Investigator, and unlikely related to DTX401 by the Sponsor ([Table 36](#)).
- Twenty-six subjects from the DTX401 Registrational Dose group experienced at least 1 serious TEAE, and for 5 subjects, the events were considered related to DTX401 by the Investigator and included 2 TEAEs of IRRs (assessed as related by the Sponsor), 1 TEAE of hyperlactacidemia (assessed as unrelated to DTX401 and related to prednisolone by the Sponsor), and 2 TEAEs of hypertriglyceridemia (1 event described above; the other event was assessed unlikely related by the Sponsor, and considered related to study participation by both Investigator and Sponsor) (Section [8.2.4.2](#)).
- Two serious events of IRRs were experienced by 2 pediatric subjects, and a causal relationship with DTX401 was established; IRRs are considered an important identified risk and ADR for DTX401. Since the implementation of risk minimization measures (slow, staged infusion and premedication), 17 subjects have been dosed with DTX401 with no additional events of IRRs reported (Section [8.2.4.5](#)).
- Hepatic reactions are considered an important identified risk and ADR for DTX401. Events of hepatic reactions most often occurred within the first 15 weeks following DTX401 administration. These events were associated with predominantly nonserious, mild (Grade 1) to moderate (Grade 2) increased liver transaminases that generally resolved or improved with corticosteroid treatment. Abnormal values in ALT and AST generally returned to the subject's baseline or within normal limits within the first year after DTX401 administration (Section [8.2.4.5](#), Section [8.2.4.7](#)).
- Nausea is considered an ADR for DTX401. TEAEs of nausea were nonserious, mostly mild (Grade 1) to moderate (Grade 2), and transient, with half of the events occurring within 2 to 14 days of DTX401 administration (average: approximately 7 days), prior to initiating prednisolone ([Table](#)).
- Four subjects overall experienced 4 serious TEAEs of hypertriglyceridemia, 2 of which were assessed as related to DTX401 by the Investigator. All serious TEAEs were assessed as unrelated to DTX401 by the Sponsor, and due to either history of hyperlipidemia and associated complications, underlying GSDIa, viral infections, or low or excessive cornstarch or carbohydrate intake (Section [8.2.4.5](#)).
- TEAEs of adrenal insufficiency (associated with corticosteroid administration) were reported in 7 subjects, including 2 subjects who experienced serious events. After risk minimization measures were implemented, no further serious events of adrenal insufficiency have been reported (Section [8.2.4.5](#)).

- A higher proportion of pediatric subjects experienced serious TEAEs. These included 3 serious TEAEs of hypertriglyceridemia, 2 serious DTX401-related TEAEs of IRRs, and 2 serious prednisolone-related TEAEs of adrenal insufficiency. Since the implementation of risk minimization measures for IRRs and adrenal insufficiency, no further events have been reported or identified in the pediatric population (Section 0, Section [8.2.4.5](#)).
- Development of anti-AAV8 antibodies was observed in all subjects following DTX401, remaining positive on long-term follow-up, and positive anti-AAV8 antibody titers were not associated with any long-term safety outcomes. There was no apparent impact of anti-G6Pase antibodies on the safety of DTX401. The clinical significance of treatment-emergent low-titer anti-G6Pase antibodies is not known (Section [8.2.4.11](#)).

#### The Applicant's Position:

The totality of available safety data from completed and ongoing clinical studies including 52 DTX401-treated subjects shows that DTX401 was well tolerated and has an acceptable safety profile across all evaluated doses including the registrational dose of  $1.0 \times 10^{13}$  GC/kg. The important identified risks of hepatic reactions and IRRs were effectively managed with risk minimization measures. No new or unexpected safety findings were observed during long-term follow-up, indicating that there are no new latent toxic events and that the safety profile of DTX401 does not change over time. Events of hypertriglyceridemia observed after DTX401 treatment likely represent the complexity of hypertriglyceridemia in GSDIa and associated challenges of dietary and cornstarch management.

#### The FDA's Assessment:

The integrated safety database for DTX401 includes 58 patients across two clinical studies: 46 patients from the Phase 3 study (DTX401-CL301; follow-up through Week 96) and 12 patients from the Phase 1/2 study (401GSDIA01; follow-up through Week 52). FDA considers the safety database adequate to characterize the safety profile of DTX401 for this rare disease with significant unmet medical need.

The safety review focused primarily on the PEAP of Study DTX401-CL301, with comparative safety data between the DTX401 and placebo groups informing section 6 of the USPI. Crossover period safety data were considered supportive only and were not used to inform the USPI. Safety data from Study 401GSDIA01 were reviewed to provide additional context for the safety profile characterized in the Phase 3 study.

In Phase 3 Study DTX401-CL301, TEAEs were reported in all 21 DTX401-treated patients (100%) compared to 22 of 25 placebo patients (88.0%) during the PEAP, with total event counts of 329 and 218, respectively. There were no deaths. SAEs were more frequent in the DTX401 group (8/21 patients, 38.1%; 10 SAEs) compared to placebo (3/25 patients, 12.0%; 4 SAEs).

Seven serious adverse reactions (SARs) were observed including anaphylaxis (2), adrenal insufficiency (2), high lactate levels (2), and hypoglycemia (1).

The most common adverse reactions occurring in  $\geq 10\%$  of patients with higher frequency in the treatment group during PEAP in Phase 3 study are presented below.

**Table 43: FDA –**

| TEAE                                 | GENGLYCOS (N=21) |                | Placebo (N=25) |                |
|--------------------------------------|------------------|----------------|----------------|----------------|
|                                      | Events n         | Subjects N (%) | Events n       | Subjects N (%) |
| ALT/AST Enzyme elevated <sup>1</sup> | 29               | 15 (71)        | 6              | 3 (12)         |
| Nausea                               | 12               | 8 (38)         | 10             | 4 (16)         |
| Headache                             | 11               | 5 (24)         | 9              | 3 (12)         |
| Hypertriglyceridemia <sup>2</sup>    | 10               | 6 (29)         | 2              | 2 (8)          |
| Adrenal Insufficiency <sup>3</sup>   | 7                | 5 (24)         | 0              | 0              |
| Gastroenteritis                      | 9                | 6 (29)         | 7              | 7 (28)         |
| Constipation                         | 5                | 4 (19)         | 0              | 0              |
| Hyperglycemia <sup>4</sup>           | 5                | 3 (14)         | 0              | 0              |
| Acne / Dermatitis Acneiform          | 4                | 4 (19)         | 0              | 0              |
| Cushingoid Features                  | 3                | 3 (14)         | 0              | 0              |
| Anaphylaxis <sup>5</sup>             | 2                | 2 (10%)        | 0              | 0              |

Source:

1 All events were mild to moderate ( $< 5.0 \times$  ULN), except one severe (Grade 3) asymptomatic event (peak ALT: 253 U/L). ALT/AST elevations peaked between 4 and 12 weeks post-administration and resolved within 15 weeks [see Warnings and Precautions (5.2)]

2 All events were mild to moderate (less than  $2.5 \times$  ULN)

3 Two SAEs were reported [see Warnings and Precautions (5.3)]

4 All events were mild to moderate

5 Two SARs with onset within minutes of GENGLYCOS administration [see Warnings and Precautions (5.1)]

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; DRT, Dorsal Root Toxicity

The safety profile was characterized by three primary safety signals occurring in DTX401-treated patients:

- **Anaphylaxis/Infusion-Related Reactions:** Two Grade 3 anaphylactic reactions (9.5%) occurred within 1 to 6 minutes of infusion initiation, both requiring immediate discontinuation and resolving with management.
- **Hepatic Toxicity:** Transaminase elevations were the most prominent treatment-emergent finding, occurring in 15 of 21 DTX401 patients (71.4%) compared to 3 of 25 placebo patients (12.0%). 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.
- **HPA Axis Suppression/Adrenal Insufficiency:** Adrenal insufficiency TEAEs occurred exclusively in 5 DTX401-treated patients (23.8%), including 2 clinically significant SAEs requiring acute medical intervention and hospitalization, one of which necessitated ICU admission.

Additionally, metabolic worsening was observed at higher rates in the DTX401 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 DTX401 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. Specifically, liver enzyme elevations, HPA axis suppression (adrenal insufficiency), and

metabolic instability or worsening were observed in both studies. Notably, no clinically significant infusion reactions were reported in the Phase 1/2 study.

### 8.3 Conclusions and Recommendations

#### The FDA's Assessment:

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 hypoglycemia which can have life-threatening consequences if untreated including seizures, coma, and death. 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.

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  $1.0 \times 10^{13}$  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 (SE) difference of -31% (-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 0.9 dose (SD 1.4, 0.4) 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.

The reduction in percent of cornstarch intake is a surrogate efficacy endpoint, reasonably likely to predict long-term 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). A Postmarketing

Requirement (PMR), to be completed within 5 years post-approval, will verify this clinical benefit through a 2-year follow-up period. The study will assess total daily cornstarch doses, fasting tolerance (TTH), nighttime cornstarch doses, metabolic biomarkers (triglycerides, uric acid, and lactate), and clinician-reported assessments of overall health.

The safety database includes (35 adults, 20 pediatric patients aged 8-17 years) exposed to the proposed commercial dose of GENGLYCOS and followed up to 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 DTX401 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.

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

## 9 FDA CONSULTATIONS

### FDA Assessments:

#### **Center for Drug Evaluation and Research (CDER)**

During the BLA review process, the clinical team consulted and engaged in substantive discussions with the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) in CDER to facilitate comprehensive understanding of the endocrine subject matter.

#### **Center for Devices and Radiological Health (CDRH)**

The clinical team requested CDRH's expert consultation on the use of the Dexcom G6 Continuous Glucose Monitor (CGM) as a measurement tool in the Phase 3 clinical study (DTX401-CL301) for DTX401. CDRH noted that the Dexcom G6 CGM was used in the DTX401 Phase 3 study to monitor glucose levels in GSDIa patients, even though the device is only FDA-approved for people with diabetes, which making its use in this study off-label. CDRH also flagged that CGM devices are less accurate at low glucose levels (below 70 mg/dL), which is precisely the range that matters most for detecting hypoglycemia in GSDIa patients. In addition, CDRH noted that CGM-based measures like time-in-range and time-below-range have not been validated as clinical endpoints, meaning they cannot be used to make formal efficacy claims about the drug. CDRH did not view the off-label CGM use as a fundamental impediment to the validity of the study data. In summary, CDRH's view is that CGM data from this study can be reported as supportive, descriptive information, but should not be the foundation for regulatory efficacy conclusions.

## 10 Advisory Committee Meeting and Other External Consultations

### The FDA's Assessment:

The BLA was not referred to an Advisory Committee Meeting as no issues were identified that would benefit from external expert advice or discussion.

## 11 Pediatrics

### The Applicant's Position:

See Section [8.1.1.6.8](#).

### The FDA's Assessment:

FDA concurs.

## 12 Labeling Recommendations

Data/Applicant's Position: This is an original application. Please see annotated label in Module 1.14.1 for proposed labeling. Not applicable.

### The FDA's Assessment:

Following negotiations, FDA and the Applicant reached agreement on the United States Prescribing Information (USPI), with revisions incorporated. See final agreed-upon USPI.

## 13 Risk Evaluation and Mitigation Strategies (REMS)

### The FDA's Assessment:

A risk evaluation and mitigation strategy (REMS) is not required to ensure safe and effective use of GENGLYCOS in the indicated population as all identified risks can be adequately mitigated through labeling, post-marketing safety surveillance, and a long-term safety observational study.

## 14 Postmarketing Requirements and Commitments

### The FDA's Assessment:

#### **Postmarketing Requirement**

1. Conduct an adequate and well-controlled clinical study to verify and describe the clinical benefit of pariglasgene brecaaparvovec-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).

Draft Protocol Submission: October 31, 2026

Final Protocol Submission: December 31, 2026

Interim Study Enrollment/Status Report #1: August 31, 2027

Interim Study Enrollment/Status Report #2: August 31, 2028

Interim Study Enrollment/Status Report #3: August 31, 2029

Interim Study Enrollment/Status Report #4: August 31, 2030

Study Completion: August 31, 2031

Final Study Report Submission: December 31, 2031

## Postmarketing Commitments

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).

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

3. Conduct adequate analytical and clinical validation studies to support revisions to the labeling of pariglasgene breccaparvovec-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 breccaparvovec-opnr is indicated.

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

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement.

4. Ultragenyx commits to reassessing the acceptance criteria for release testing of pariglasgene breccaparvovec-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

## 15 Appendices

### 15.1 References

#### Applicant's References

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## 15.2 Financial Disclosure

### The Applicant's Position:

Information on financial disclosures for Studies 401GSDIa01, 401GSDIa02, and DTX401-CL301 are provided in the tables below. A complete list of investigators and statements of due diligence are described in Module 1.3.4.

### **Covered Clinical Study: 401GSDIa01**

|                                                                                                         |                                         |                                                           |
|---------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                          | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: 19                                                            |                                         |                                                           |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 |                                         |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0            |                                         |                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                              |                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------------------------------------|
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u></p> <p>Significant payments of other sorts: <u>N/A</u></p> <p>Proprietary interest in the product tested held by investigator: <u>N/A</u></p> <p>Significant equity interest held by investigator in study: <u>N/A</u></p> <p>Sponsor of covered study: <u>N/A</u></p> |                              |                                                         |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Yes <input type="checkbox"/> | No <input checked="" type="checkbox"/> (Not applicable) |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Yes <input type="checkbox"/> | No <input checked="" type="checkbox"/> (Not applicable) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                              |                                                         |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Yes <input type="checkbox"/> | No <input checked="" type="checkbox"/> (Not applicable) |

**Covered Clinical Study: 401GSDIa02**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: 18                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                           |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |                                                           |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u></p> <p>Significant payments of other sorts: <u>N/A</u></p> <p>Proprietary interest in the product tested held by investigator: <u>N/A</u></p> <p>Significant equity interest held by investigator in study: <u>N/A</u></p> <p>Sponsor of covered study: <u>N/A</u></p> |                                         |                                                           |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Yes <input type="checkbox"/>            | No <input checked="" type="checkbox"/> (Not applicable)   |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Yes <input type="checkbox"/>            | No <input checked="" type="checkbox"/> (Not applicable)   |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                           |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Not applicable)              |

**Covered Clinical Study: DTX401-CL301**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                         |                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)                   |
| Total number of investigators identified: <u>94</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                                                                             |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |                                                                             |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |                                                                             |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u><br>Significant payments of other sorts: <u>N/A</u><br>Proprietary interest in the product tested held by investigator: <u>N/A</u><br>Significant equity interest held by investigator in study: <u>N/A</u><br>Sponsor of covered study: <u>N/A</u> |                                         |                                                                             |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Yes <input type="checkbox"/>            | No <input checked="" type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input type="checkbox"/>            | No <input checked="" type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>3</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                                                                             |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant)            |