Results from a pivotal phase 3 double-blind placebo-controlled trial of DTX401 for the treatment of individuals with glycogen storage disease type Ia (GSDIa)

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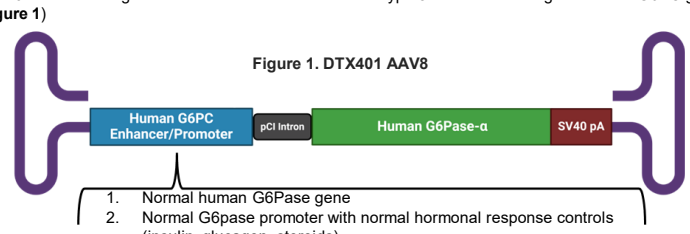
INTRODUCTION

- GSDIa is a rare, potentially life-threatening inherited carbohydrate metabolism disorder caused by biallelic pathogenic *G6PC* gene variants, resulting in deficiency of the glucose-6-phosphatase complex[1,2]
- DTX401 is an investigational adeno-associated virus serotype 8 vector containing the human *G6PC* gene (**Figure 1**)

Figure 1. DTX401 AAV8



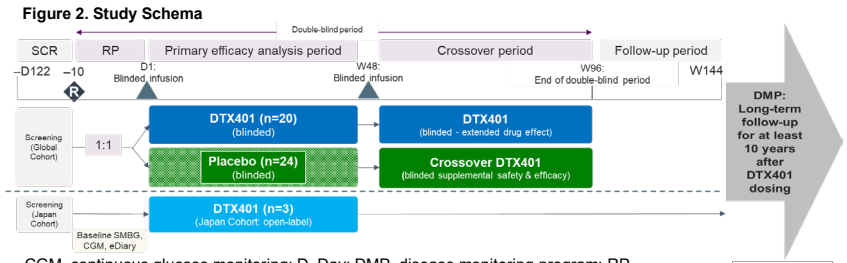
OBJECTIVES

- The primary objective of the study was to evaluate the efficacy of DTX401 to reduce or eliminate dependence on exogenous glucose replacement therapy needed to maintain glucose control

METHODS

- DTX401-CL301 (GlucoGene Study; NCT05139316), is an ongoing, pivotal, phase 3, double-blind, randomized, placebo-controlled trial of DTX401 in patients 8 years and older with GSDIa
- Participants were randomly assigned (1:1) to receive blinded DTX401 or placebo
- After the 48-week PEAP, participants crossed over in a blinded manner (DTX401 at Day 1 received placebo and placebo at Day 1 received DTX401 at Week 48 [Crossover Placebo]) in an additional 48-week blinded Crossover Period (**Figure 2**)

Figure 2. Study Schema



CGM, continuous glucose monitoring; D, Day; DMP, disease monitoring program; RP, randomization period; SCR, screening - all participants underwent nutrition optimization and stabilization before randomization and stability was an eligibility criterion for randomization and dosing with blinded IP; SMBG, self-monitoring blood glucose; W, week.

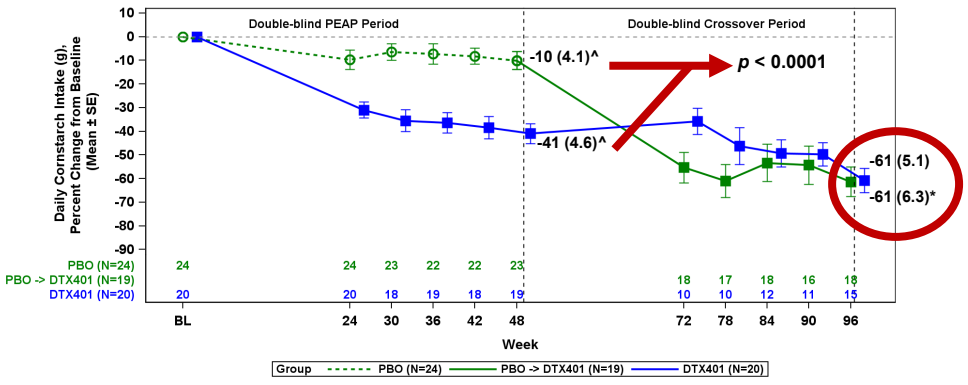
Primary endpoint: Percent change from Baseline to Week 48 in daily cornstarch intake for DTX401 versus placebo

Secondary endpoints:
- Change from Baseline to Week 48 in number of total daily doses of cornstarch
- Change from Baseline to Week 48 in percentage of glucose values in hypoglycemic range (< 70 mg/dL)
- Patient Global Impression of Change (PGIC) assessment score at Week 48

Key eligibility criteria included:
- 8 years of age and older
- Documented GSDIa with confirmation by molecular testing or enzymatic activity on liver biopsy
- No detectable preexisting antibodies to the AAV8 capsid
- No history of liver transplant or significant liver disease

RESULTS

Figure 3. Statistically Significant and Clinically Meaningful Cornstarch Reductions With Continued Reductions After Week 48



^Least-squares mean (SE) shown for Week 48. *Placebo group participants re-baselined at Week 48 and change in Crossover DTX401 reflects mean (SE) change from Week 48.

- 61% cornstarch reduction at Week 96 exceeded desired cornstarch reduction from baseline clinical trial interviews of 45% supporting clinical meaningfulness of this change

Table 1. Statistically Significant Reduction at Week 48 in Number of Daily Cornstarch Doses, Mean (SE)

	Week 48	Week 96
Placebo (n=24)	-0.1 (0.1)	-
DTX401 (n=20)	-1.1 (0.2)^	-1.9 (0.4)
Crossover DTX401* (n=19)	-	-1.6 (0.5)

^*p*-value = 0.0011 for DTX401 versus Placebo at Week 48. *Placebo group participants were re-baselined at Week 48 and change in Crossover DTX401 reflects change from Week 48.

Table 2. Statistically Significant Reduction at Week 48 in Nighttime Cornstarch

	Group	Week 48	Week 96
Percent Change in Nighttime Intake, Mean (SE)	Placebo	+15.16 (27.66)	-
	DTX401	-42.48 (7.80)†	-70.23 (10.02)
	Crossover DTX401	-	-75.05 (7.56)
Change in Number of Nighttime Doses, Mean (SE)	Placebo	+0.5 (0.4)	-
	DTX401	-0.4 (0.2)‡	-0.8 (0.2)
	Crossover DTX401	-	-1.1 (0.5)
Elimination of at Least One Nighttime Dose, percentage of participants	Placebo	7	-
	DTX401	50§	67
	Crossover DTX401	-	67

°Participants who reported using nighttime cornstarch at baseline are included. †Nominal *p*-value=0.0132 for DTX401 versus Placebo at Week 48. ‡Nominal *p*-value = 0.0105 for DTX401 versus Placebo at Week 48. §Nominal *p*-value = 0.031 for DTX401 versus Placebo at Week 48.

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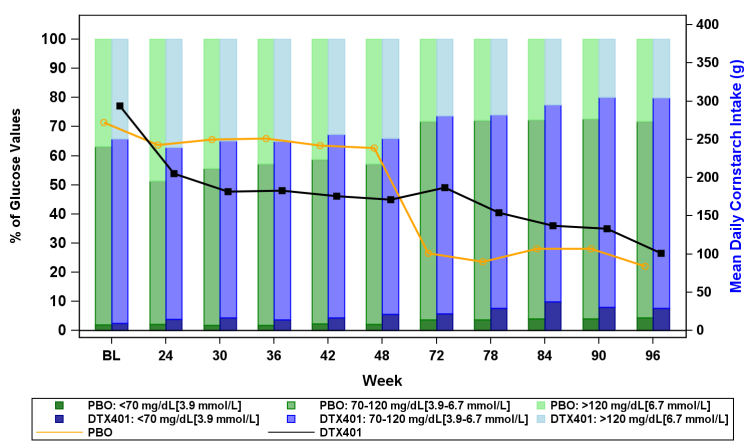
- Anne Blake, Deepali Mitragotri, and Andrew Grimm are employees and shareholders of Ultragenyx
- Ultragenyx provided medical writing assistance in the preparation of this presentation

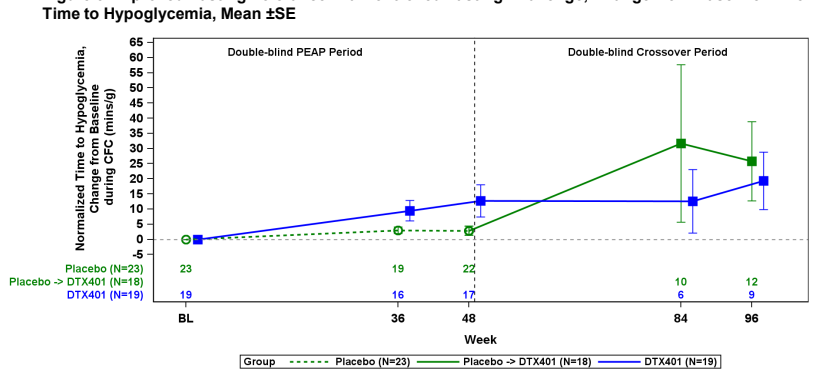
RESULTS (Continued)

Figure 4. Low Levels of Hypoglycemia With Improved Euglycemia, Mean Percentage of Glucose Values <70, 70-120, and >120 mg/dL based on CGM



- Low rates of hypoglycemia, improved time in euglycemic range (70-120 mg/dL), despite daily cornstarch intake reduction

Figure 5. Improved Fasting Tolerance in a Controlled Fasting Challenge, Change from Baseline in Normalized Time to Hypoglycemia, Mean ±SE



Normalized TTH (minutes/gram) was calculated as TTH (minutes) divided by the amount of pre-controlled fasting challenge (CFC) cornstarch (grams). Placebo group participants were re-baselined at Week 48 and change in Crossover DTX401 reflects change from Week 48. Evaluation of TTH and normalized TTH were predefined analyses following evaluation of fasting tolerance in the DTX401 Phase 1/2 study.

Japan Cohort: Experience to Date
- As of study Week 24 in three participants treated DTX401 open-label in Japan:
  - Similar large reductions in daily cornstarch intake, mean (SE) reduction 95% (4.8)
  - Two completely off cornstarch at Week 24, third completely off cornstarch at Week 36
  - Mean (SE) percentage glucose values < 70 mg/dL at baseline 3.67 (3.47) and 0.53 (0.29) at Week 24; mean (SE) reduction of 3.13 (3.73)
  - No serious adverse events

Improved Patient-reported Quality of Life

Patient Global Impression of Change (PGIC)
- At Week 48, 79% (15/19) reported improved GSDIa in DTX401-treated group vs 52% (12/23) Placebo
- At Week 96 (end of Double-blind Crossover Period) improved GSDIa reported in:
  - 83% (10/12) DTX401 group
  - 95% (18/19) Crossover DTX401 group

Patient interviews
- At Week 48, 39% reported improved ability to self-regulate blood sugar levels (eg, feeling of a "safety net") in DTX401 versus 18% Placebo
- At both Week 48 and Week 96, DTX401-treated participants most frequently reported:
  - Reductions in cornstarch intake
  - Less hypoglycemia
  - Less tiredness
  - Improvements in physical function, social, and diet/daily regimen impacts

Safety Summary

Important Identified Risks:
- Hepatic reactions
  - Aminotransferase elevations (ALT, AST) were most frequently reported TEAEs
  - Most were nonserious, transient, managed with tapering course of oral corticosteroids
- Infusion-related reactions (IRRs)
  - Two Grade 3 SAEs resulted in termination of DTX401 infusion; resolved with treatment, no clinical sequelae
  - After risk minimization measures implemented, no additional IRRs reported or identified

Important Potential Risks (based on AAV gene therapy class effects):
- Dorsal root ganglion/peripheral nerve effects, insertional mutagenesis/malignancy, thrombotic microangiopathy – No events observed after DTX401

Potentials Risks:
- Hypertriglyceridemia
  - TEAEs of hypertriglyceridemia in 20 (50%) of DTX401-treated subjects
  - Most nonserious, mild (Grade 1) or moderate (Grade 2) in severity
  - Triglyceride elevations not associated with pancreatitis or clinical sequalae of atherosclerotic disease

Table 3. Change from Baseline in Lactate, Alanine, Uric Acid, and Triglycerides, Mean (SD)

	Group	Week 48	Week 96
Pre-CFC Whole Blood Lactate, mmol/L	Placebo	0.79 (2.55)	-
	DTX401	1.14 (1.62)	1.51 (1.90)
	Crossover DTX401	-	0.39 (2.64)
Pre-CFC Plasma Alanine, µmol/L	Placebo	48.31 (160.07)	-
	DTX401	-6.95 (171.39)	4.04 (233.81)
	Crossover DTX401	-	3.19 (116.95)
Plasma Uric Acid, mg/dL	Placebo	-0.22 (1.57)	-
	DTX401	0.62 (1.42)	0.85 (2.57)
	Crossover DTX401	-	0.58 (1.17)
Triglycerides, mg/dL	Placebo	7.4 (179.8)	-
	DTX401	209.8 (383.1)	245.3 (322.6)
	Crossover DTX401	-	231.0 (346.2)

CONCLUSIONS

- **A single dose of DTX401 resulted in:**
  - **Substantial daily cornstarch intake reduction of 41-61%, improving further over time**
  - **Reduction in cornstarch dose frequency, including at night**
  - **Improved glucose regulation within 70-120 mg/dL range and maintained low levels of hypoglycemia**
  - **Improved quality of life reported**
- **DTX401 was well tolerated with an acceptable safety profile**
- **Long-term DTX401 efficacy and safety to be collected in GSDIa Disease Monitoring Program**

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