



Investor Conference Call

ASGCT Data Presentations DTX401 and DTX301

May 15, 2020

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DTX401 Phase 1/2 Study in Glycogen Storage Disease Type Ia (GSDIa)

Confirmatory Cohort 3 Data

AAV8-mediated Liver-directed Gene Therapy as a Potential Therapeutic Option in Adults with Glycogen Storage Disease Type Ia (GSDIa): Results From a Phase 1/2 Clinical Trial

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A Phase 1/2 Global, Open-label, Dose Escalation Trial of DTX401 in Adult GSDIa Patients

DTX401 is an adeno-associated virus serotype 8 (AAV8) vector that expresses the human *G6PC* gene under the transcriptional control of the normal G6Pase promoter

3 Subjects per Cohort:

- Cohort 1: 2.0×10^{12} GC/kg (July 2018)
- Cohort 2: 6.0×10^{12} GC/kg (Jan 2019)
- Cohort 3: 6.0×10^{12} GC/kg (Oct 2019)

Key Study Assessments Include:

- **Time to Hypoglycemia:** Duration of symptom-free euglycemia (glucose ≥ 60 mg/dL or 3.33 mmol/L) during controlled fasting challenge
- **Cornstarch Dosing:** Impact on dietary supplementation with cornstarch
- **Hepatic Glycogen Content:** Measured by MRI fat fraction

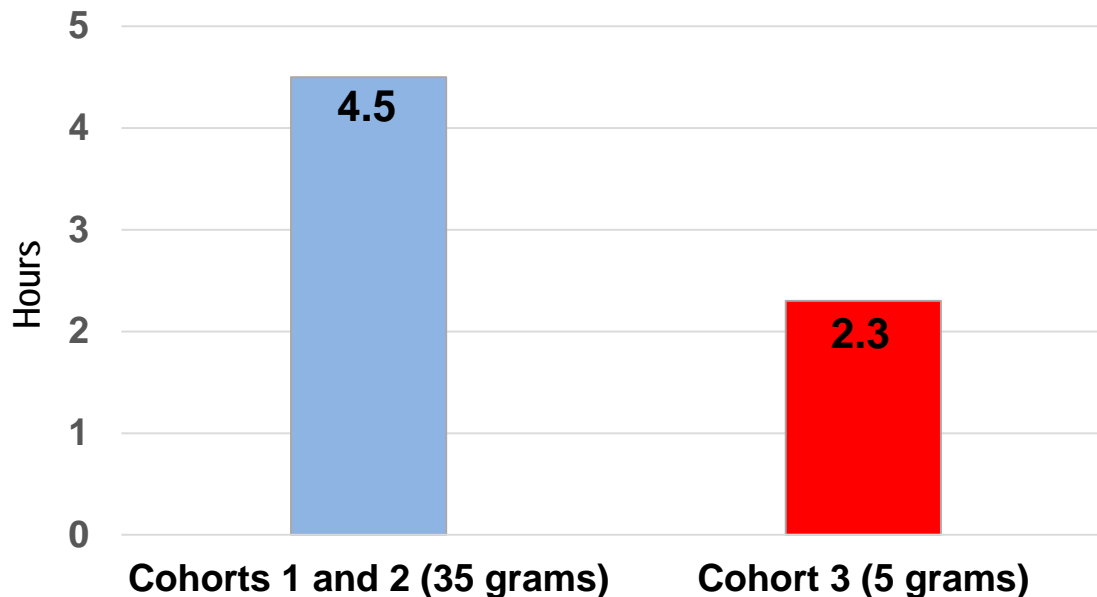
Cohort 3: Treatment Protocol Changes

Lessons learned from earlier cohorts prompted the following changes to the protocol prior to dosing of patients in Cohort 3 (6×10^{12} GC/kg):

- Reduced cornstarch dose at the start of the controlled fasting challenge (decreased from 35 grams to 5 grams)
- Use of continuous glucose monitoring (CGM)
- Implementation of an 'optimized' reactive steroid regimen

Cohort 3 Baseline Time to Hypoglycemia 48% Less Than Baseline of Prior Cohorts Due to Disease Severity and Modified Protocol

Mean duration of baseline controlled fasting challenge, hours

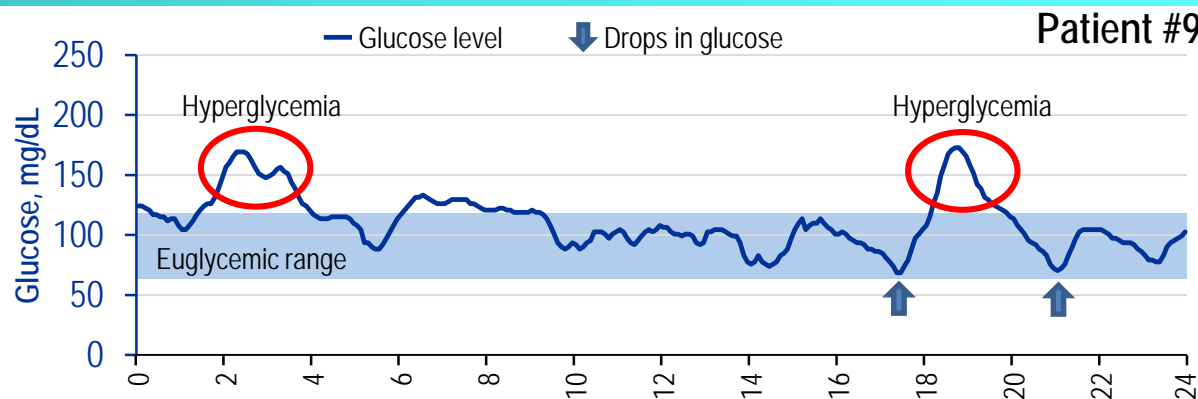


- Reduced cornstarch dose at the start of the controlled fasting challenge in Cohort 3 avoided hyperinsulinemic responses observed in Cohorts 1 and 2

Early Transgene Expression Revealed by CGM Data

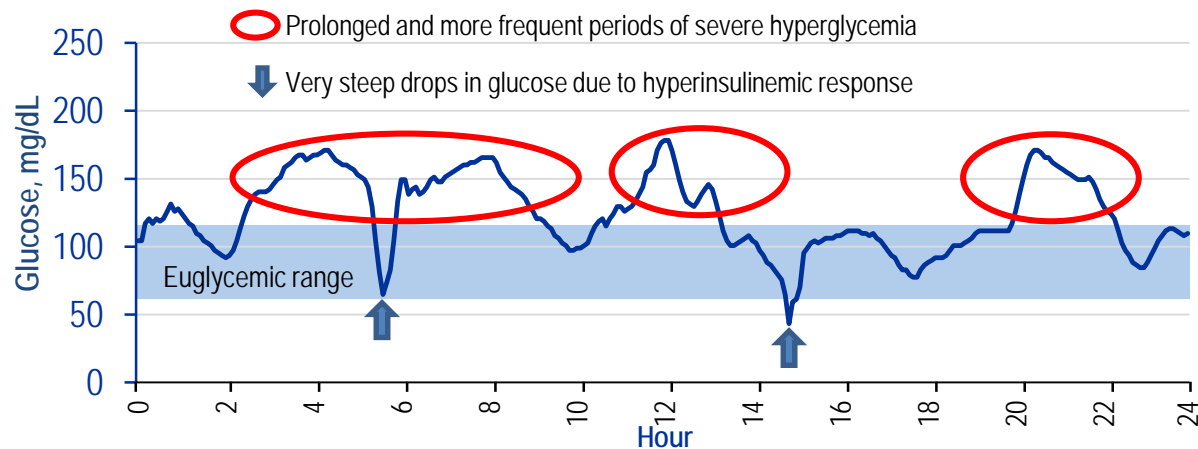
Day -3 Prior to DTX401 Dose

- Periods of hyperglycemia followed by drops in glucose

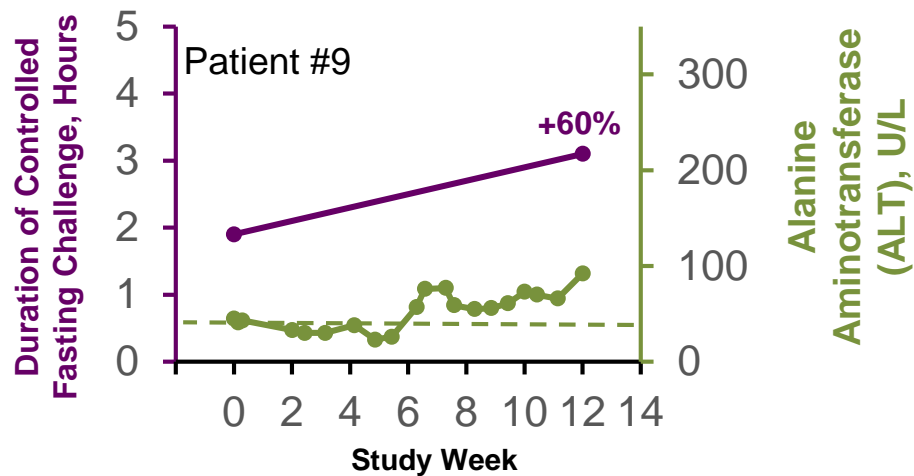
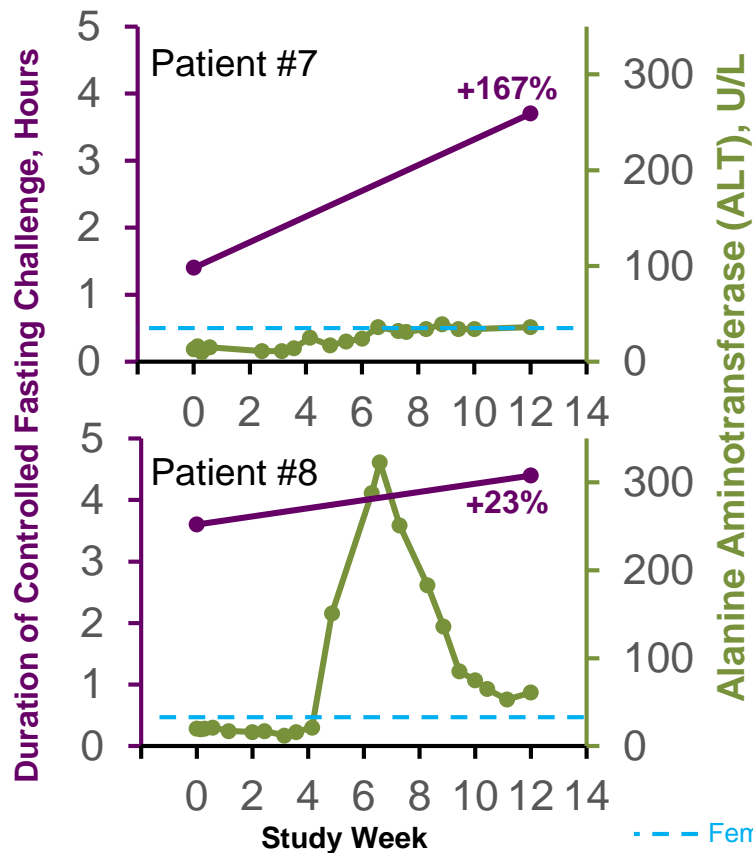


Day +4 After DTX401 Dose

- As transgene expression begins post-DTX401 dose, prolonged periods of severe hyperglycemia are followed by hyperinsulinemic responses resulting in severe drops in glucose



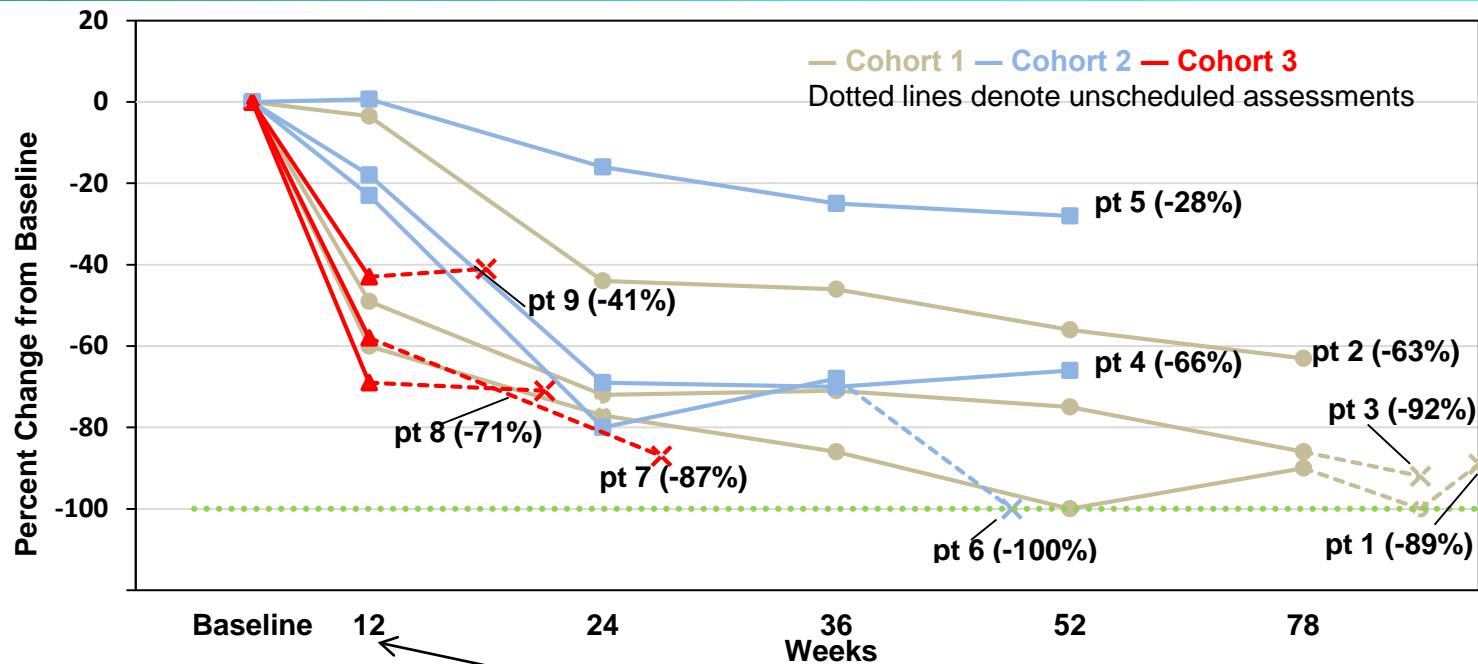
All Patients in Cohort 3 Experienced Increased Time To Hypoglycemia



- All three patients received an optimized reactive steroid regimen at approximately week 4
- Patient 8 had an asymptomatic and transient rise in ALT

Substantial Reduction in Cornstarch Requirements for all Patients

More Rapid Reductions in Cohort 3 by 12 weeks



Week 12 Mean Reduction in Cornstarch

Cohort 1	38%
Cohort 2	14%
Cohort 3	57%

Patient 3: Significantly Less Cornstarch Needed After Receiving DTX401

Pre-Treatment



75% reduction of cornstarch needed for an 11-day trip



Further reduced by Week 85 (92% reduction)

12 Months Post-Tx



Conclusion: Confirmatory Cohort Data

Cohort 3

- More rapid reductions in cornstarch requirements
- CGM confirms early transgene expression and allows for timely and more accurate cornstarch reduction
- 'Optimized' reactive steroid regimen more effectively mitigated ALT elevations

All Cohorts

- All patients (n=9) have shown an improved response in time to hypoglycemia and decreased cornstarch requirements
- Consistent and acceptable safety profile across all patients

DTX401: Next Steps

- Collecting longer-term data from confirmatory Cohort 3
- Planning for Phase 3 study and continuing FDA discussions
 - Cornstarch requirements, time to hypoglycemia during fast challenge, number of hypoglycemic events through CGM data, all important in evaluating glucose control

**Longer-term Cohort 3 data
expected in second half of 2020¹**

¹ barring potential delays due to COVID 19



DTX301 Phase 1/2 Study in Ornithine Transcarbamylase (OTC) Deficiency

Cohort 1-3 Data Update

DTX301: Six of Nine Patients Responding Now Including all 3 Patients in Cohort 3

- **Cohort 3: Responses from all three patients**

- Patient 7: Complete responder (off NH₃ scavenger drugs and diet)
- Patient 8: Responder (discontinued one of two ammonia scavengers and modified diet)
- Patient 9: Confirmed Responder (confirmed at week 24, not yet tapered medication or diet)

- **Cohorts 1 and 2: Long-term follow-up of complete responders**

- Ureagenesis greater than 100% for 2 years and 1.5 years, respectively
- Restricted protein diet and alternate pathway drugs discontinued for more than one year
- Ammonia maintained within normal parameters throughout the long-term follow-up period
- Excellent clinical condition with no significant adverse events, hospitalizations, or events related to urea cycle disorders

DTX301: Responses Observed in All Dose Cohorts and Three Responders at Cohort 3 Dose

Cohort / Dose (GC/kg)	Patient # (Gender) / Follow-Up Duration	% Change in Ureagenesis (baseline → after treatment, % normal ¹)	% Change in Ammonia Levels (baseline → after treatment, umol/L)	Alternate Pathway Medication and Diet Status	Response Status
Cohort 1 (2x10 ¹² dose)	1 (Male) 130 Weeks	+53% (67% → 102%)	Normal levels maintained	Off medications Liberalized diet	Complete responder³
	2 (Female) 104 Weeks	+6% (52% → 55%)	92% decrease (146 → 11)	No change	No response
	3 (Male) 104 Weeks	+81% (48% → 87%)	Normal levels maintained	No change	No response
Cohort 2 (6x10 ¹² dose)	4 (Male) 78 Weeks	+79% (66% ⁴ → 118%)	Normal levels maintained	Off medications Liberalized diet	Complete responder³
	5 (Female) 78 Weeks	-38% (19% → 12%)	Normal levels maintained	No change	No response
	6 (Female) 78 Weeks	+218% (20% → 64%)	80% decrease (156 → 31 [Week 78])	Tapering medication Liberalizing diet	Responder
Cohort 3 (1x10 ¹³ dose)	7 (Female) 52 Weeks	+79% (24% → 44%)	Normal levels maintained	Off medications Liberalized diet	Complete responder³
	8 (Female) 36 Weeks	?% ² (66% → 25%)	90% decrease (184 → 19 [Week 24])	Increased protein intake and discontinuation of one of two ammonia scavengers	Responder (consistent ammonia reduction; clinical benefit noted)
	9 (Male) 24 Weeks	+188% (25% ⁴ → 73%)	Normal levels maintained	No change yet	Responder (confirmed) (still on steroids)

¹ Normal rate of ureagenesis = 300 umol*kg/hr. ² Aberrant high baseline ureagenesis values inconsistent with patient clinical severity making ureagenesis not interpretable.

DTX301: Next Steps

- Enrolling three additional patients in prophylactic steroid cohort at 1e13 dose
 - Dosing in this cohort is currently on hold due to COVID-19
- Planning for Phase 3 study and continuing FDA discussions
 - Ammonia expected to be a primary endpoint based on FDA feedback

**Prophylactic steroid cohort (1e13 dose) update
expected in second half of 2020¹**

¹ barring potential delays due to COVID 19