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Positive Cohorts 1 & 2 Results From The Phase 1/2, AAV8-mediated Liver-directed Gene Therapy Trial In Glycogen Storage Disease Type Ia (GSDIa)

First presentation of Cohort 2 data

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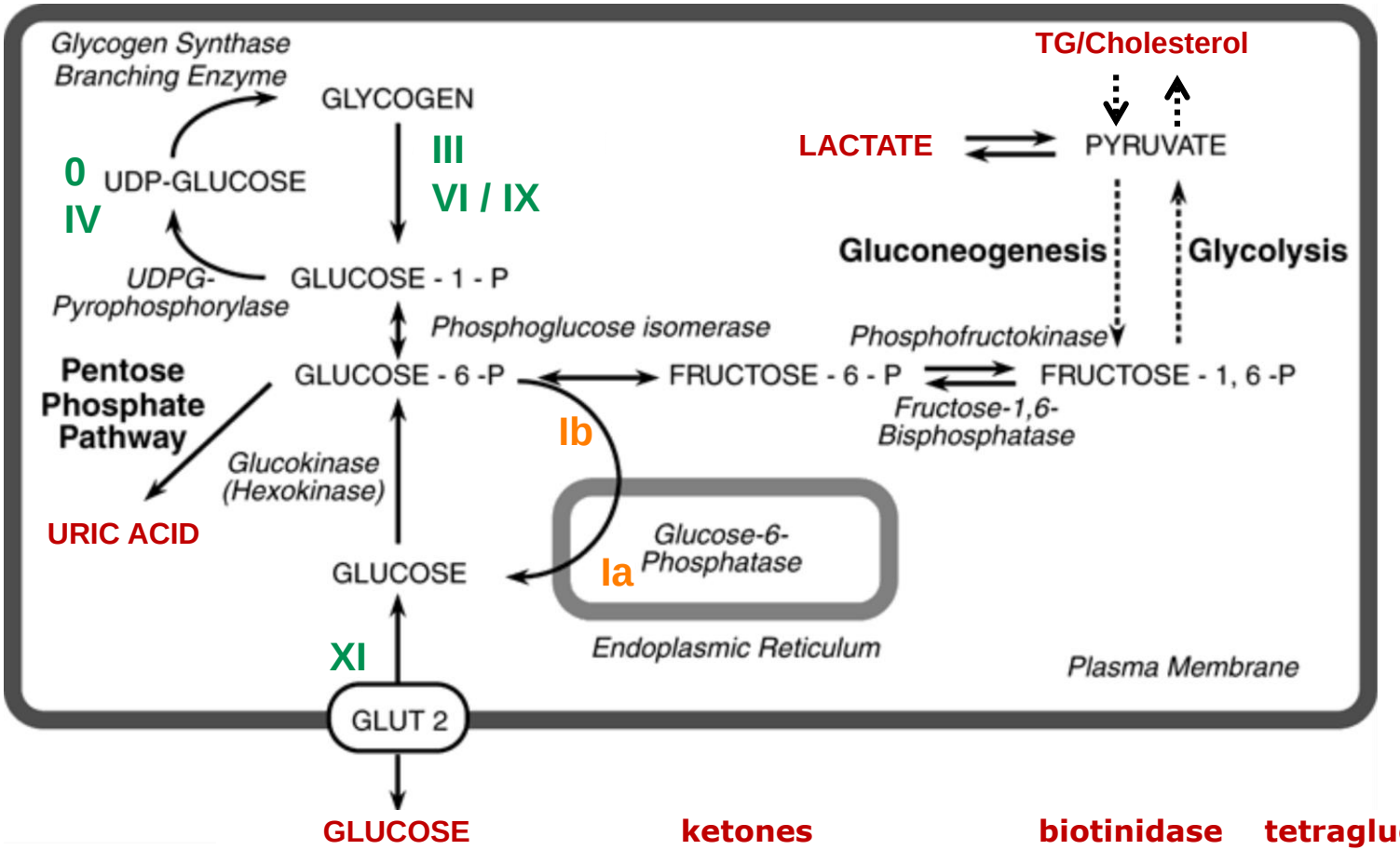
Disclosures

- I am employed by an academic institute which implies unmentioned potential conflicts of interest.
- I have confidentiality agreements with several pharmaceutical and medical food companies.
- I am local PI in sponsor-initiated clinical trials, for which the UMCG has received grants/research support:
  - NCT03517085 - Safety and Dose-Finding Study of DTX401 (AAV8G6PC) in Adults With Glycogen Storage Disease Type Ia (GSDIa) sponsored by Ultragenyx Pharmaceutical Inc.
  - NCT02318966 - Glycosade v UCCS in the Dietary Management of Hepatic GSD (Glyde) sponsored by Vitaflo International, Ltd.
- I am PI in investigator-initiated research, for which the UMCG has received a research grant by Alfasigma Nederland BV.
- I have performed consultations for Danone, Sigma-Tau BV and Dimension Therapeutics, Inc, (acquired by Ultragenyx Pharmaceutical).
- **Dr. Derks has a policy that all contracts are via the UMCG Contract Research Desk and all honoraria are paid to UMCG/RuG.**

ASAT/ALAT CK pre-albumin



GLUCOSE ketones biotinidase tetraglucoside

Adapted from: Chen ea. OMMBID online.

Guidelines for GSDIa

Eur J Pediatr (2002) 161: S112–S119
DOI 10.1007/s00431-002-1016-7

ORIGINAL PAPER

Jan Peter Rake · Gepke Visser · Philippe Labrune
James V. Leonard · Kurt Ullrich · G. Peter A. Smit

Guidelines for management of glycogen storage disease type I – European Study on Glycogen Storage Disease Type I (ESGSD I)

Eur J Pediatr (2002) 161: S120–S123
DOI 10.1007/s00431-002-1017-6

ORIGINAL PAPER

Gepke Visser · Jan Peter Rake · Philippe Labrune
James V Leonard · Shimon Moses · Kurt Ullrich
Udo Wendel · G. Peter A. Smit

Consensus guidelines for management of glycogen storage disease type 1b – European Study on Glycogen Storage Disease Type 1

 ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics

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What are therapeutic aims for GSDIa patients?

avoid **hypoglycemia** …. neuroglycopenia
avoid **hepatomegaly** …. ( )
avoid **counterregulation** …. negative effects of counterregulatory hormones
… lactic acidosis
… growth
… obesity
… adenoma
… muscle mass, motor development

avoid **secondary effects** …. hypertriglyceridemia ….. pancreatitis
…..hyperuricemia ….. gout
…. osteopenia (pH+dietary calcium restriction 2nd to lac restriction)

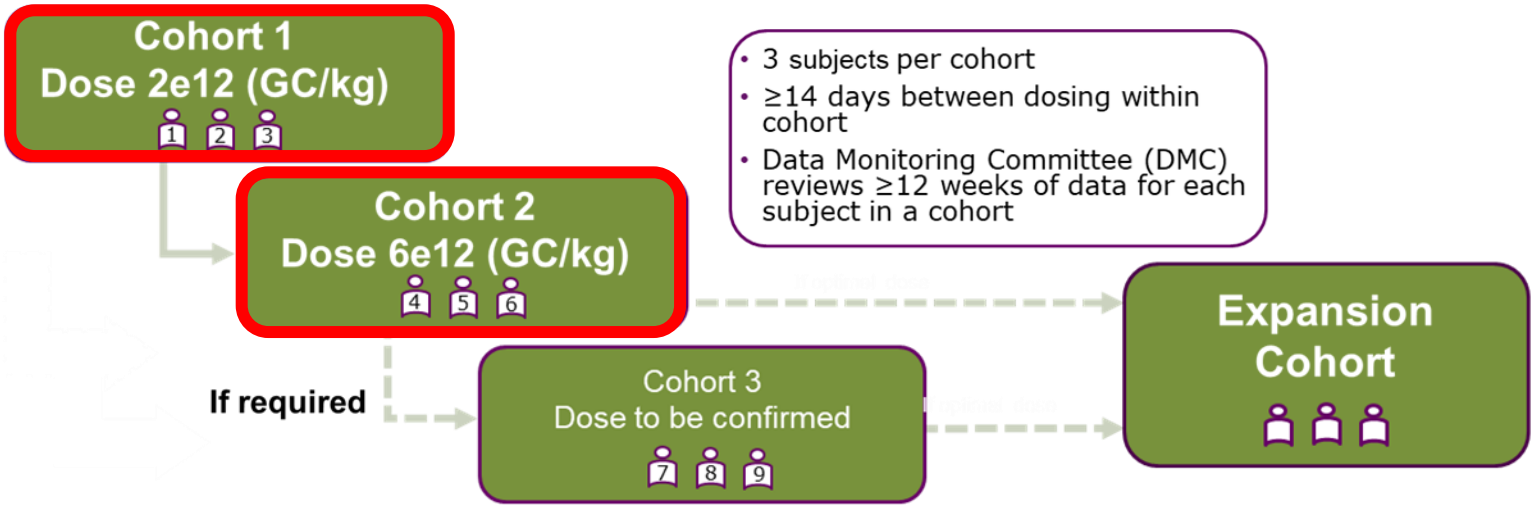
avoid **long-term complications**
…. renal disease
…. polycystic ovaries
…. adenoma … anemia, malignant changes
…. seizure disorder

Courtesy of René Santer

Novel AAV vector and Study Design for the treatment of GSDIa

DTX401 is an AAV8 vector that expresses the human G6PC under the transcriptional control of a liver specific promoter.

GSD Ia Phase 1/2 Gene Therapy Study: A Global Multi-center Open-label Dose Escalation Trial



Study Population and Study Assessments

I/E Criteria

Inclusion

- Males and females ≥18 years of age
- GSDIa confirmed by molecular testing
- Documented history of ≥1 hypoglycemic event with blood glucose <3.33 mmol/L (60 mg/dL)

Exclusion

- Liver transplant
- ALT or AST >ULN; TG ≥1000 mg/dL (11.3 mmol/L)
- Anti-AAV8 neutralizing antibody titer ≥1:5
- Presence of liver adenoma >5 cm or liver adenoma >3 cm and ≤5 cm in size that has annual growth rate of ≥0.5 cm per year

Assessments

- Duration of symptom-free euglycemia (glucose ≥ 3.33 mmol/L or 60 mg/dL) during fasting
- Impact on requirement for dietary supplementation with cornstarch
- Effect on hepatic glycogen content as measured by MRI
- Effect on hyperlipidemia and uric acid levels
- Impact on the patient's quality of life and sleep

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Study Demographics

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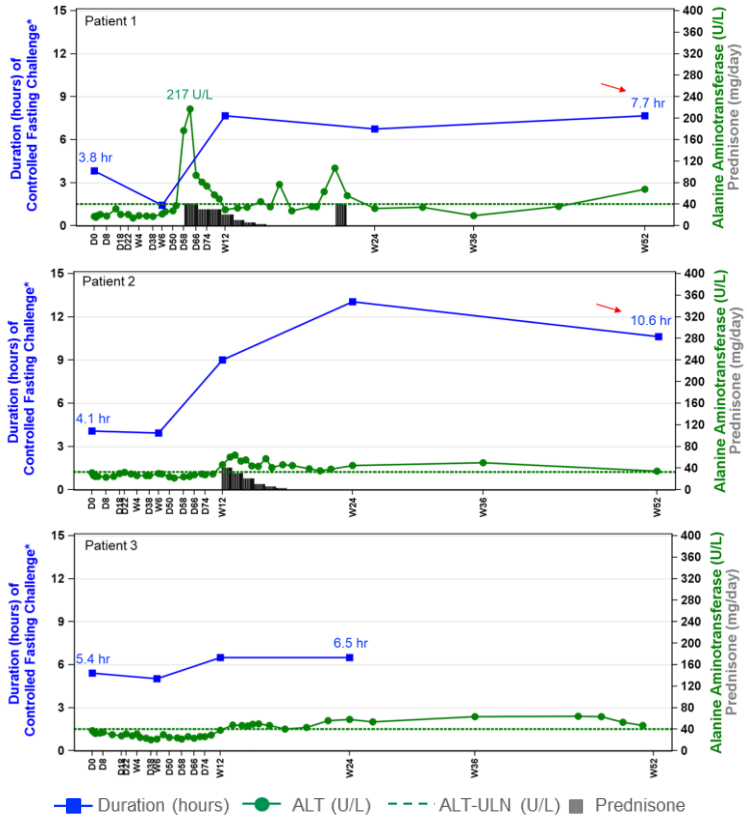
	Cohort 1 (2e12 GC/kg)			Cohort 2 (6e12 GC/kg)		
	Pt 1	**Pt 2**	**Pt 3**	**Pt 4**	**Pt 5**	**Pt 6**
Study Site	UCONN	UMICH	UCONN	UT	UMICH	UCONN
Gender	Male	Female	Male	Male	Male	Male
Age (yrs)	28	57	51	31	19	39
Genotype	c.247C>T c.1039C>T	c.1039C>T (homozygous)	c.247C>T c.1039C>T	c.379_380dup (homozygous)	c.247C>T c.323C>T	c.79del c.189G>A
Weight (kg)	57	59	80	114	74	93
Total GC	1.14e14	1.19e14	1.60e14	6.00e14	4.47e14	5.58e14
Baseline Treatment	Cornstarch	Cornstarch + Continuous Feed	Cornstarch	Cornstarch	Cornstarch	Cornstarch
On Study (wks)	52	52	52	34	25	19

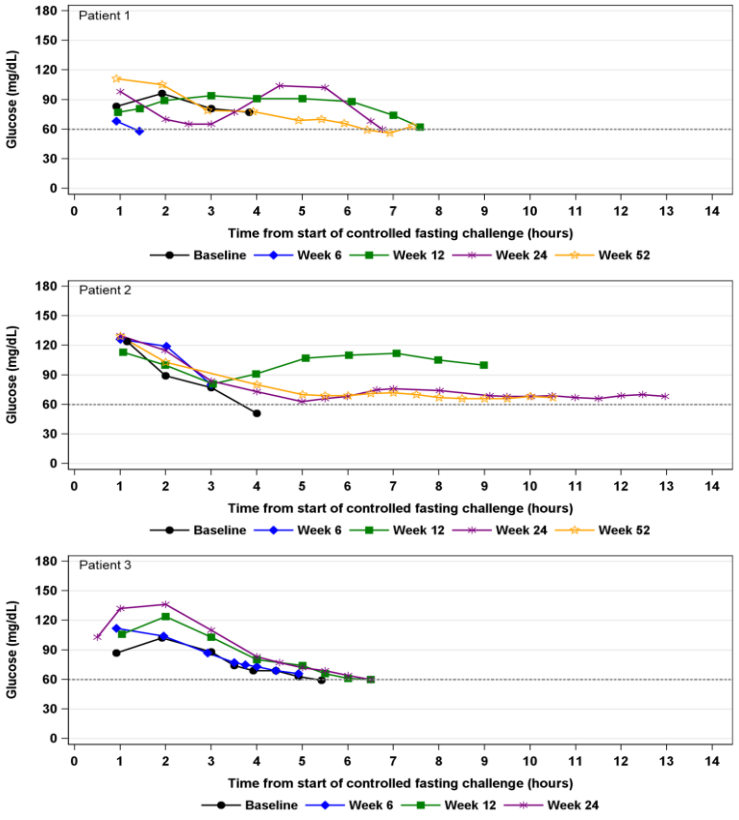
*Data Cut-off: Aug 31, 2019

Cohort 1 Long-term data demonstrates improvement in Time to Hypoglycemia

Cohort 1 (2e12 GC/kg)
Controlled Fasting Challenge



Cohort 1 (2e12 GC/kg)
Glucose Curves



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Emerging Cohort 2 demonstrating improvement in Time to Hypoglycemia

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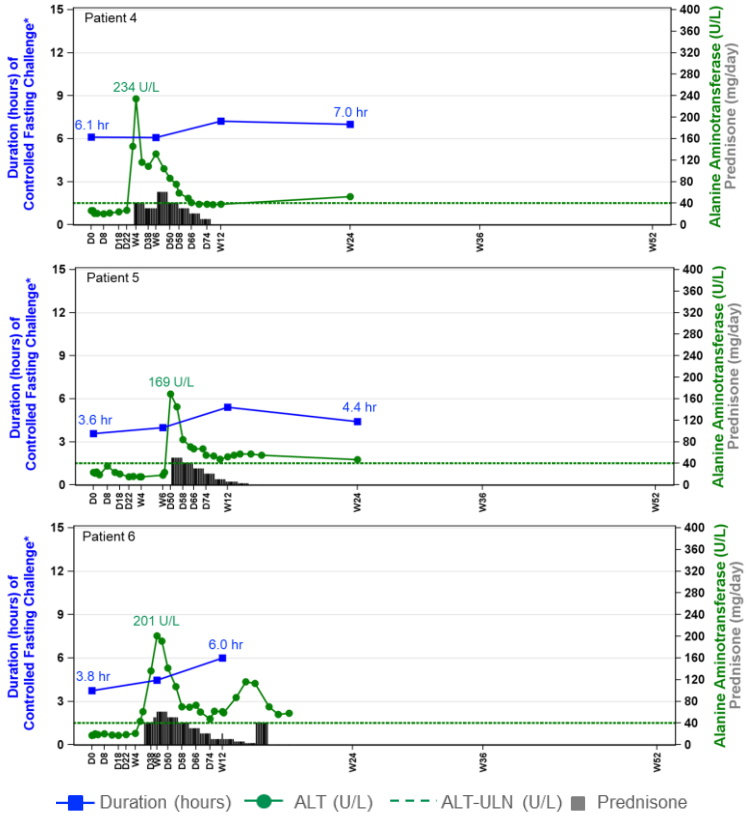
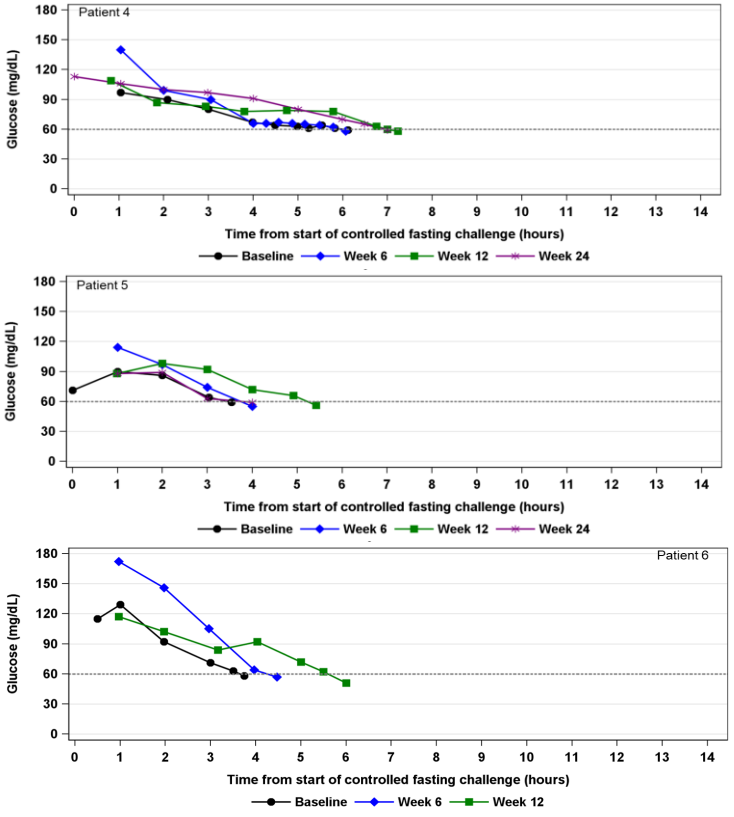
Cohort 2 (6e12 GC/kg) Controlled Fasting Challenge



Cohort 2 (6e12 GC/kg) Glucose Curves



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Cohort 2, Patient 6 Glucose curve demonstrating Insulin Surge

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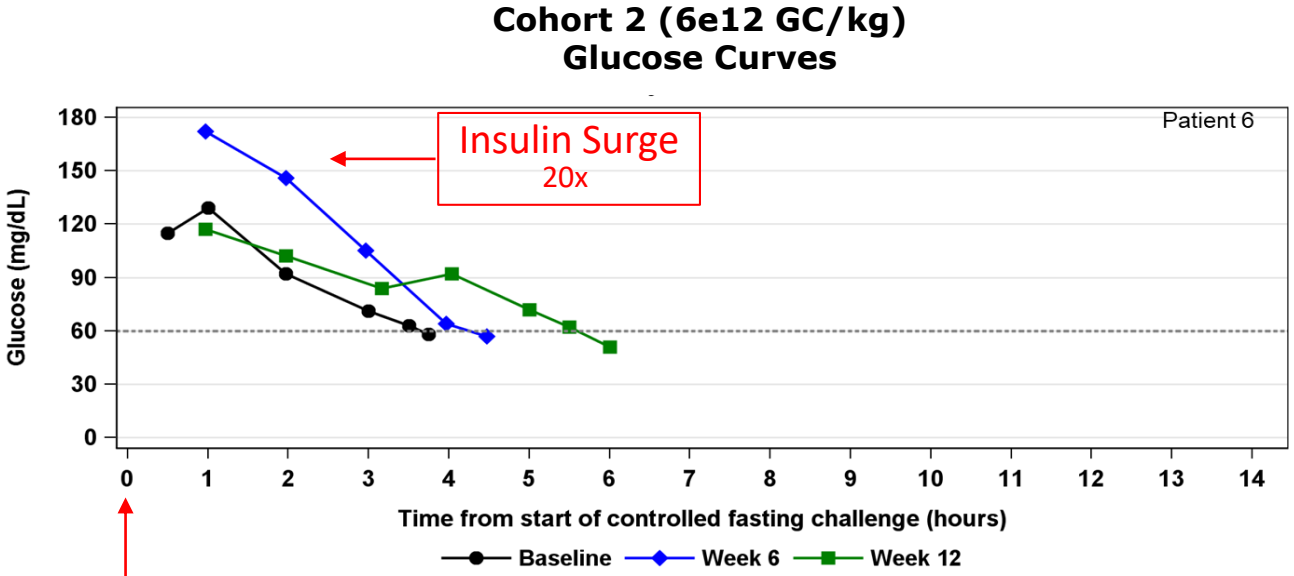

Patient 6 on steroids per protocol at W6

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Clinically Significant Reduction of Daily Cornstarch Use across both Cohorts

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	Cohort 1 (2e12 GC/kg)			Cohort 2 (6e12 GC/kg)		
Visit	**Pt 1**	**Pt 2**	**Pt 3**	**Pt 4**	**Pt 5**	**Pt 6**
BL	405	171	269	325	268	329
W6	355	165	255	270	268	341
W12	160	165	138	265	270	253
W24	94	96	76	100	224	*105
W36	56	92	78			
W52	0	76	57			
Reduction	**100%**	**56%**	**79%**	**69%**	**16%**	**68%**

*W18

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Improvements in other efficacy evaluations

- Cohort 1 longer term data:
  - Substantial reduction in daily cornstarch use
  - Significant weight loss in 2 of the 3 patients (over 20 pounds)
  - Variable improvements in lactate and reduction of liver size
- Cohort 2 data supports continued improvement in secondary GSDIA outcome measures:
  - Hyperglycemia during Controlled Fasting Challenge at W6 with evidence of Insulin surge
  - Lactate levels lower for all patients in Cohort 2 at W12 when compared to similar times at baseline
  - Liver imaging still being reviewed but patients demonstrating reduction in liver fat fraction by MRI
  - Patients self-reported improvement in quality of life

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Conclusions

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- Cohort 1 (DTX401 at 2e12GC/kg)
  - Improvement in time to hypoglycemia during a controlled fasting challenge
  - Reduction in daily cornstarch use
- Cohort 2 (DTX401 at 6e12 GC/kg) data are still emerging
  - Improvement in time to hypoglycemia during a controlled fasting challenge
  - Reduction in daily cornstarch use
  - Improvement in other clinically important measures of GSDIa
- DTX401 was well tolerated with all AEs Grade 1 (mild) or 2 (moderate) in severity; no related serious AEs in either Cohort 1 and Cohort 2
- Data Monitoring Committee reviewed cumulative safety data from Cohorts 1 and 2 and concluded it is safe to continue enrollment of patients into Expansion Cohort (DTX401 at 6e12 GC/kg)

Acknowledgements

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Allen Poma, MD	Ultragenyx Gene Therapy, Cambridge, MA, USA
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A brief history of gene therapy in GSD Ia

- 1998 – 2000: Liver cells
- 1999 – 2005: Mice
- 2005 – 2016: Dogs
- Feb 2016 and June 2017: Clinical Advisory Board (Dimension Therapeutics)
- July 2018: First GSD Ia patient (Ultragenyx)

Adeno-Associated Virus (AAV)

- Wild type AAV is not associated with disease/congenital infections in humans
- Non-integrating episomal form of vector genome establishment
- > 70% is seropositive to AAV-1 and AAV-2, 25-40% have pre-existing nAb to AAV-8
- Clinical trials:
  - hemophilia A (NCT03001830)
  - hemophilia B (NCT00979238, NCT01687608)
  - hepatitis C (NCT02315638)
  - late-onset OTC- deficiency (NCT02991144)
  - X-linked retinoschisis (NCT02317887)

GSD Ia: 4 cases

Case I: ML 20y

c.79delC p.Gln27Argfs*9

Case II: MT 20y

c.247C>T, p.Arg83Cys

Case III: RK 22 y

c.467G>T, p.Trp156Leu

Case IV: FS 11y

c.1118 C>T, p.Gln347X

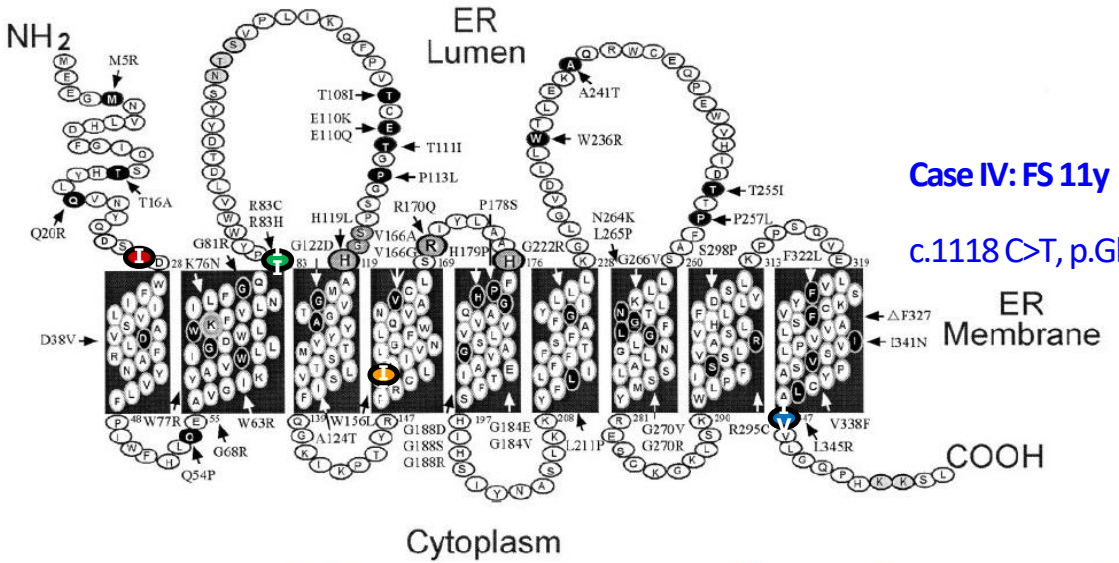

FIG. 1. **Location of missense and ΔF327 mutations identified in the *G6Pase* gene of GSD-1a patients.** Human G6Pase is anchored to the ER by nine transmembrane helices (18, 19). The mutations are indicated and shown in *black*. Amino acid residues comprising the phosphatase signature motif are denoted by *large shaded circles*.

Shieh JJ et al. JBC. 2002.