associazione italiana glicogenosi presenta

convegno nazionale glicogenosi

ventiseiesima edizione

5 - 6 ottobre 2024 Bologna

Ascoltare, accogliere,
accompagnare le persone
con glicogenosi oggi
per progettare insieme
*il **domani***

Terapia genica per la glicogenosi tipo Ia: aggiornamenti dal trial con DTX401

Dott. Alessandro Rossi
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Terapia genica per la glicogenosi tipo Ia: aggiornamenti dal trial con DTX401

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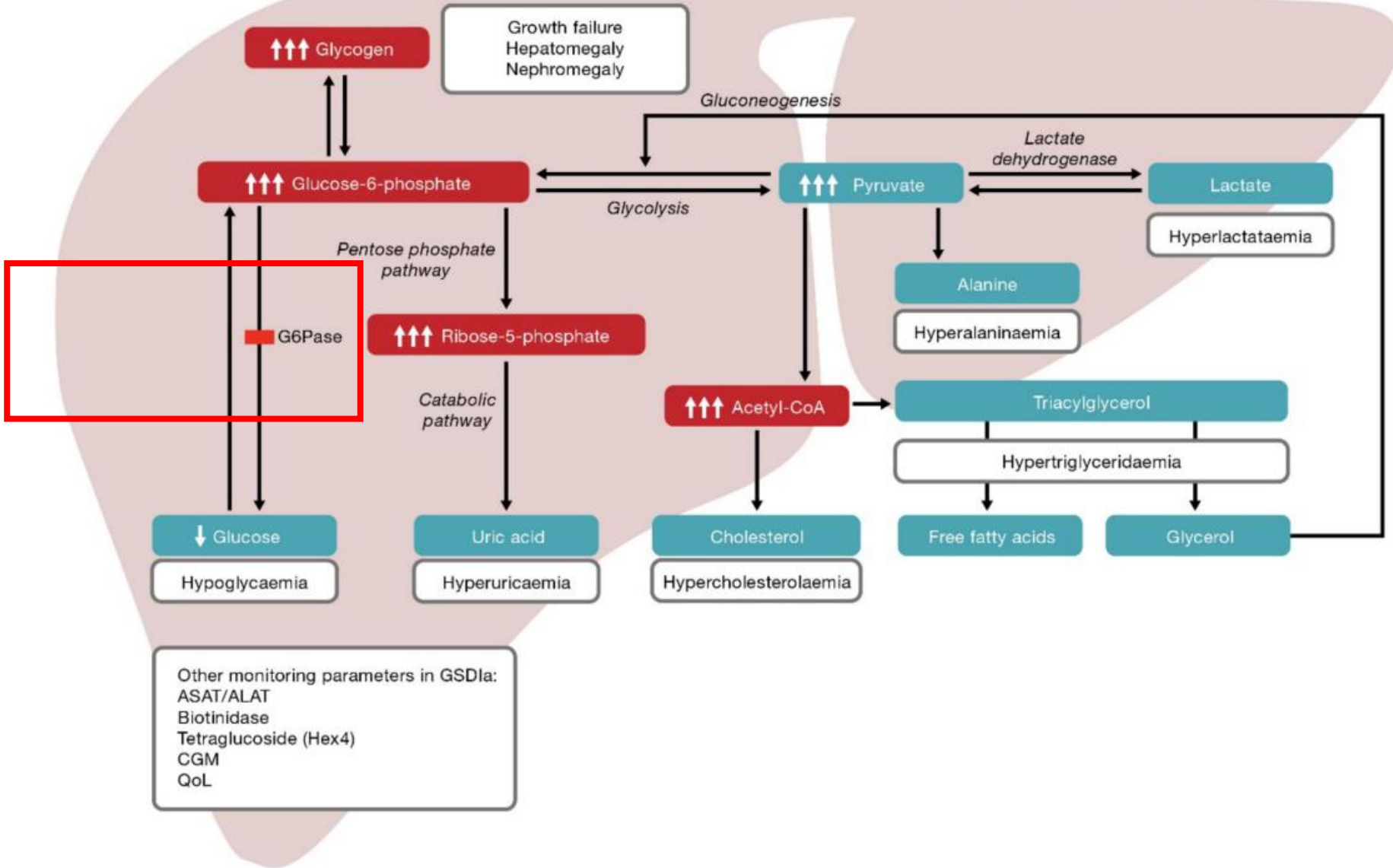
Bologna 06 Ottobre 2024

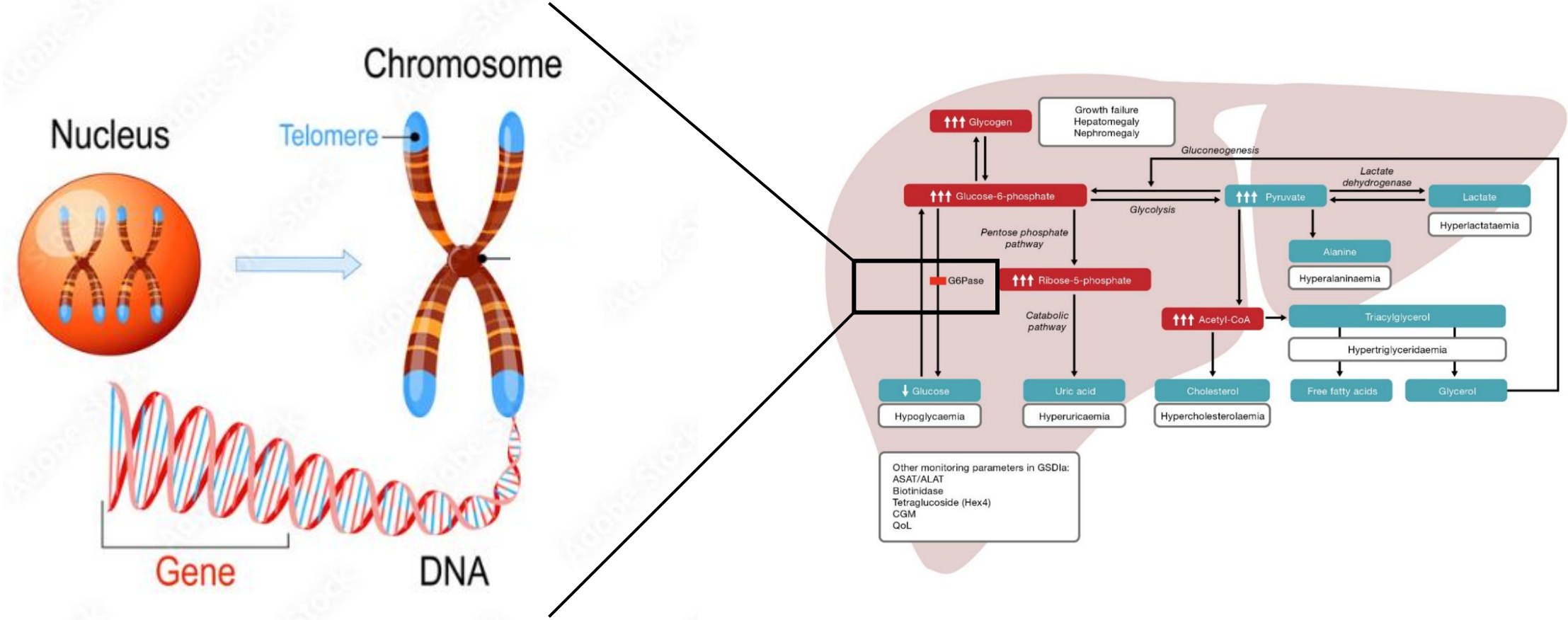
- I dati presentati sono stati raccolti nel corso di trial clinici sponsorizzati da Ultragenyx pharmaceutical Inc.
- Il sottoscritto non ha ricevuto alcun compenso per la partecipazione ai suddetti trial clinici nè per questa presentazione

Glycogen Storage Disease Type Ia (GSDIa)

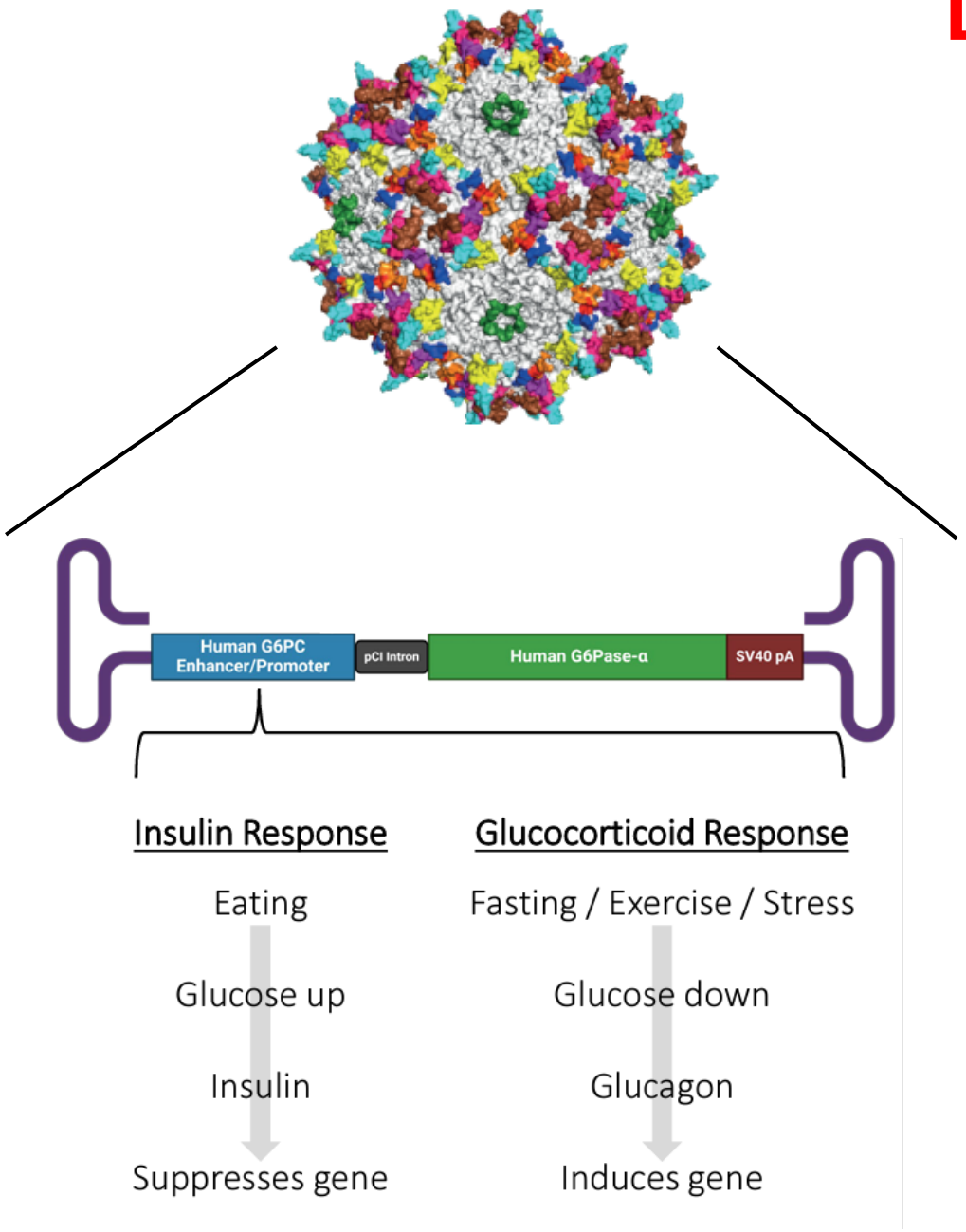


Derks, #Rossi et al. *Nutrients* 2021

Glycogen Storage Disease Type Ia (GSDIa)

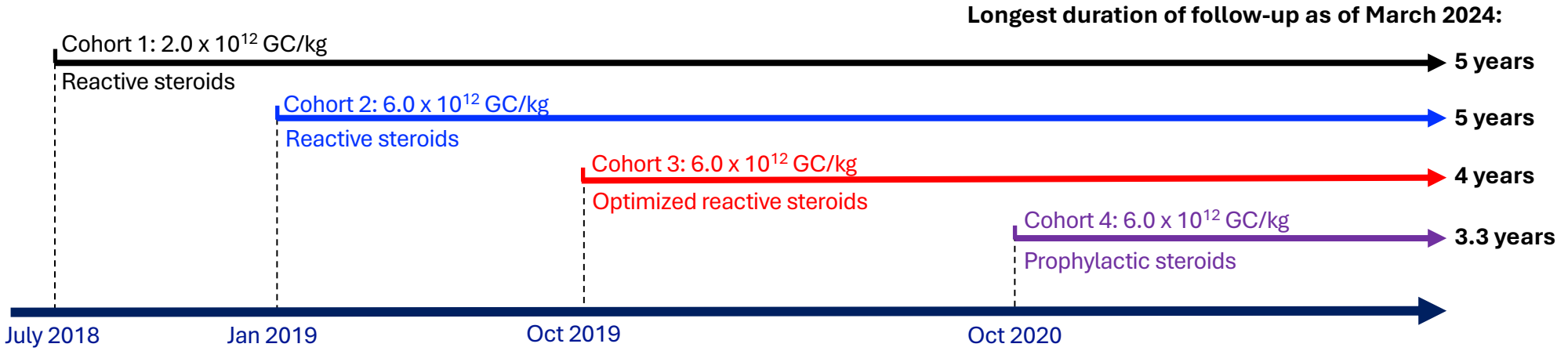


DTX401



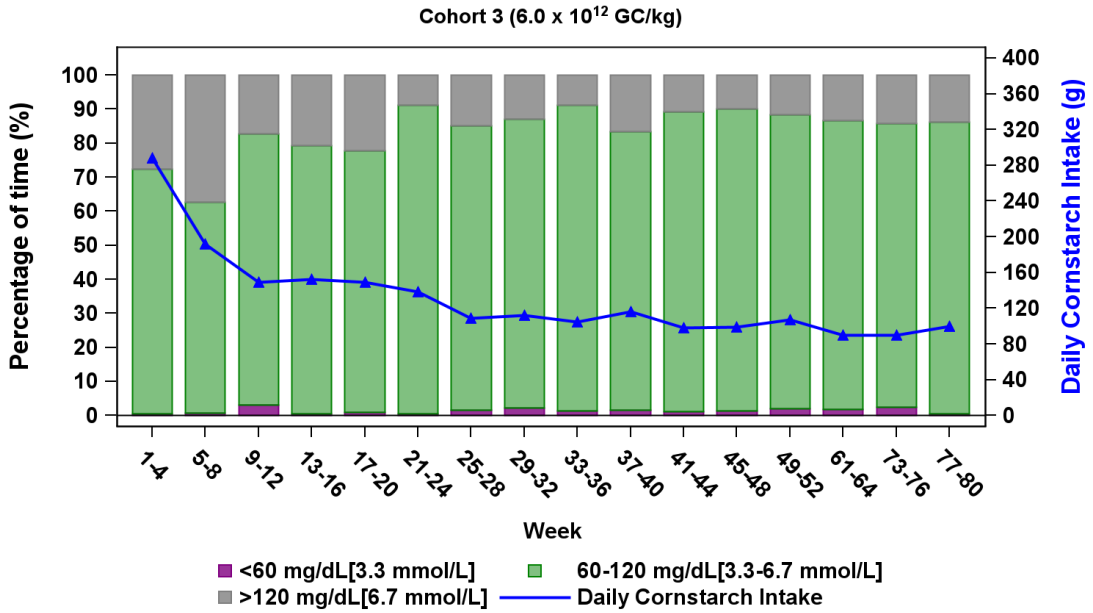
- Derives from a **non-pathogenic** AAV8 virus
- Encodes for *G6PC* sequence with native promoter and enhancer
- Transduces efficiently differentiated hepatocytes
- Long-term transduction after **single** i.v. vector administration
- Potential liver immune reaction

Phase 1/2 trial

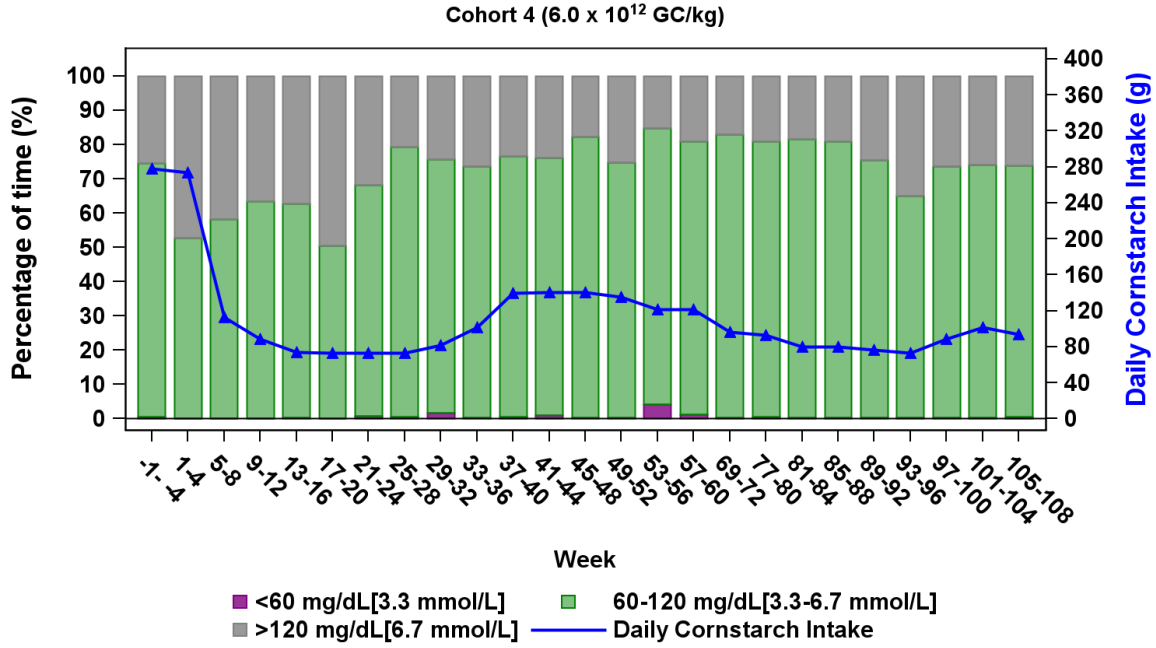


- Open label, dose-escalation
- 12 participants (4 Females, 8 Males, age > 18 years)
- Outcomes
  - Cornstarch amount and frequency
  - Percentage of time in euglycemia (60-120 mg/dL) by continuous glucose monitoring (CGM)
  - Time to hypoglycemia (TTH) assessed by a controlled fasting challenge (CFC)

Cornstarch Reduction and CGM Euglycemia (60-120 mg/dL): Improvement or Stability in Cohorts 3 and 4



- **Average cornstarch intake reduced by ~65% at Weeks 77 to 80 compared with Weeks 1 to 4, while time in euglycemia increased by ~19% in the same period**



- **Average cornstarch intake reduced by ~63% at Weeks 101 to 104 compared with Weeks -1 to -4, while time in euglycemia remained stable in the same period**

Only weeks with data from at least two participants and 5000 records from continuous glucose monitoring and three participants with cornstarch data were plotted.

Time to Hypoglycemia* (TTH)

- **In all participants (Cohorts 1–4; n = 12)**
  - Mean (SD) increase in TTH during the CFC was 4.1 (3.9) hours at the last visit
    - Mean (SD) Baseline TTH: 3.4 (1.4) hours
    - Mean (SD) Week 52 TTH: 5.2 (3.1) hours
    - Mean (SD) Last Visit TTH: 7.5 (4.1) hours

- **In the first study participants enrolled in Cohort 1 (with 4.5 to 5 years of follow up; [n = 3])**
  - Mean (SD) increase in TTH at Year 5 was 8.1 (3.6) hours, ranging from a 4.1 to 11.2-hour increase

*Modifications to the conduct of the controlled fasting challenge (used to measure TTH) included changes in pre-fasting cornstarch doses and dietary carbohydrate intake. This complicated the interpretation of TTH as an efficacy outcome parameter; however, despite the changes, we observed increases in the time to hypoglycemia in some participants.

Safety and Adverse Events*

- **Serious Adverse Events (SAEs) (n=34, of which 0 treatment-related)**
  - No participants were discontinued from the study due to an AE or died
  - No participants experienced infusion-related reactions
  - Frequently reported SAEs were gastroenteritis (4 events in 3 participants) and hypoglycemia (6 events in one participant
  - Most SAEs were CTCAE Severity Grade 2 (moderate)
- **Non-Serious TEAEs**
  - Transaminase elevations (12, 100%), resolved upon steroid treatment
  - Hypertriglyceridemia (4, 33%)
  - Hyperglycemia (3, 25%)
  - Headache (3, 25%)
- No patients experienced AAV class effects of dorsal root ganglion toxicity/peripheral nerve effects, thrombotic microangiopathy, or malignancy
- Anti-AAV8 antibodies developed for all participants by Week 52
- No participants developed anti-G6Pase antibodies

***As of 22-Mar-2024 data cutoff**
†Assessed by the Investigator

Nutritional management

Total Calories

- Mean total calories (diet and cornstarch) decreased from 2374 (1204-3645) kcals at Baseline to 2024 (950-3173) kcals at Last Visit (350 kcal reduction)
- Mean calories from cornstarch (UCCS) decreased by 793 kcals
- Mean total calories from non-UCCS diet increased by 443 kcals from Baseline to Last Visit

Body weight and BMI

- Weight decreased from Baseline to Last Visit by 1.1 kg (range: -16 kg to 9 kg)
- BMI decreased from Baseline to Last Visit by 0.5 kg/m^2 (range: –6 kg/m^2 to 3 kg/m^2)

Macronutrients

- As UCCS was reduced, non-UCCS carbohydrates, fats, and proteins were increased to maintain a balanced diet and avoid unintentional energy deficits
- The macronutrient distribution shifted total carbohydrates from 65% of total kcals at Baseline to 43% of total kcals at Last Visit

Carbohydrates

- Mean total carbohydrate from diet and UCCS decreased from 383 g at Baseline to 218 g at Last Visit (- 165 g)
- Mean total carbohydrate from UCCS decreased from 277 g at Baseline to 78 g at Last Visit (- 199 g)
- Mean total non-UCCS carbohydrate increased from 106 g at Baseline to 140 g at Last Visit(+ 34 g)

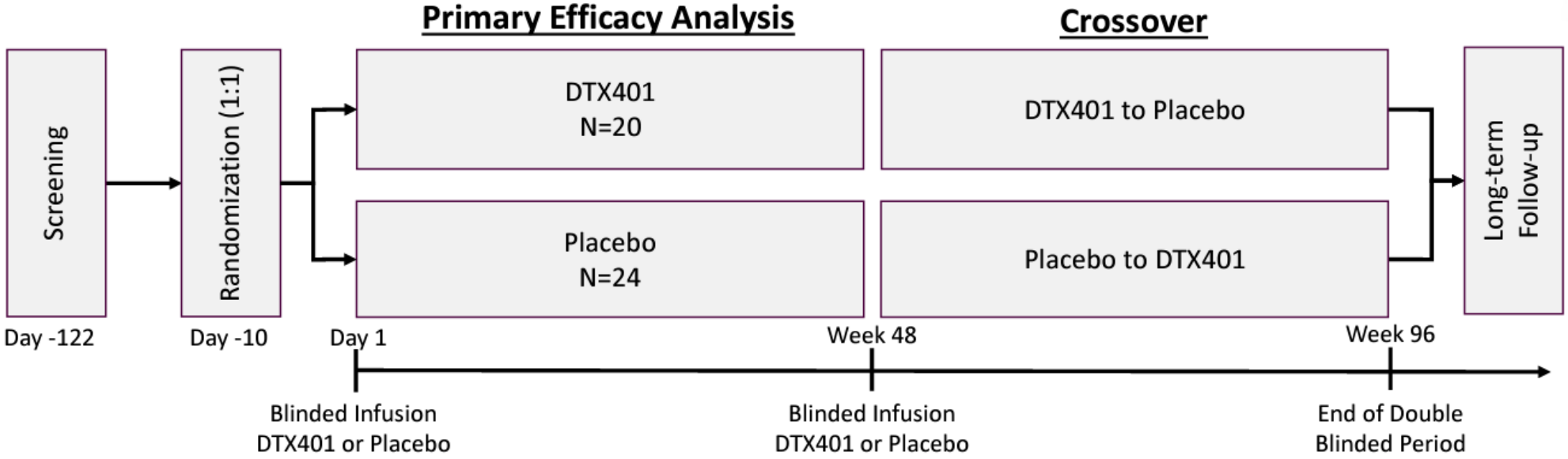
Participants needed close monitoring and support as they transitioned from a diet where UCCS was a major source of calories to a food-based diet

Patient-reported Experiences

- **Patient Global Impression of Change (PGIC):** Of nine participants with available data at Week 52, 67% (n=6) reported their GSDIa was moderately or much improved since the start of the study, correlating with a reduction in cornstarch
  (R^2 = 0.55; Spearman rank correlation coefficient = -0.77)
- **Participant interviews* at Week 24 (n=5), Week 52 (n=7), and Week 104 (n=7) showed:**
  - Most patients commonly reported improvements in glycemic control, symptoms, and function
  - While few negative changes were reported, some patients reported negative or mixed experiences (*eg*, frustration/stress) in instances of blood glucose instability, lifestyle, and diet adjustments after treatment

*Participant trial interviews recorded as study endpoint. Safety and efficacy of investigational product not yet established.

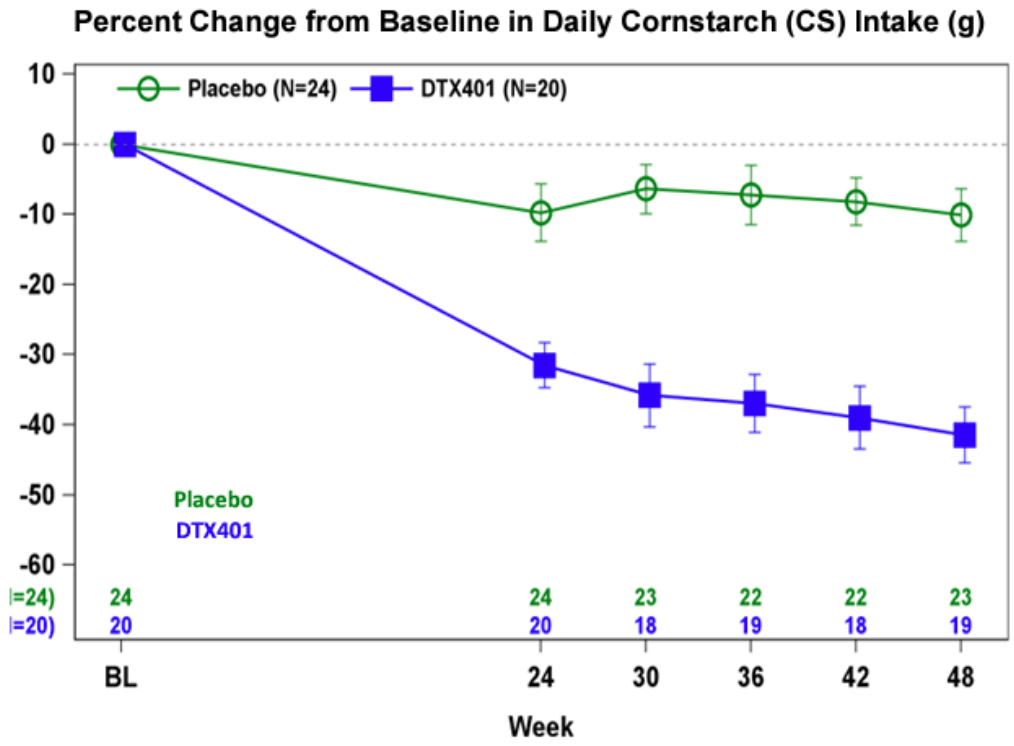
Phase 3 trial



- Randomized double blind placebo controlled
- 19 females, 25 males (26 pt > 18 years old; 18 pt 8-17 years old
- 17 study sites
- Outcomes:
  - Cornstarch amount and frequency
  - Percentage of time in euglycemia (60-120 mg/dL) by continuous glucose monitoring (CGM)
  - Time to hypoglycemia (TTH) assessed by a controlled fasting challenge (CFC)

Phase 3 trial

Persuasive statistically significant cornstarch reduction continuing through Week 48



Responder Analysis at Week 48

≥ 30% reduction in cornstarch

- 13/19 (68%) in DTX401 arm compared to 3/23 (13%) in placebo (p = 0.0003)

≥ 50% reduction in cornstarch

- 7/19 (37%) in DTX401 compared to 1/23 (4%) in placebo (p= 0.0038)

Total Daily Cornstarch (CS) Doses

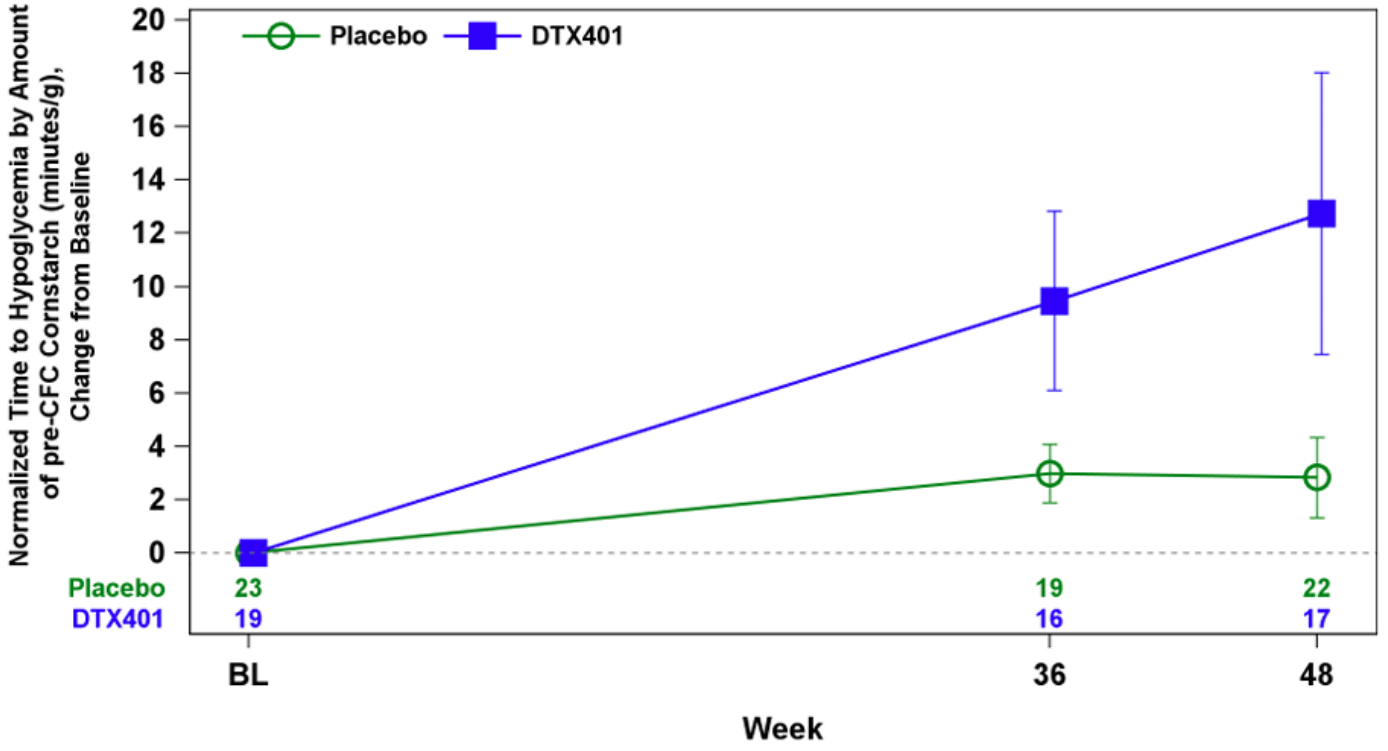
Total Daily CS Doses (n)	Placebo N=24	DTX401 N=20	p-value
Baseline Mean (SD)	5.1 (1.4)	5.8 (1.4)	
Δ BL to W48 Mean (SD)	-0.1 (0.6)	-1.1 (0.9)	
Δ BL to W48 LS Mean (SE)	**-0.2 (0.2)**	**-1.1 (0.2)**	**0.0011**

Phase 3 trial

DTX401 Showed ~5x More Improvement in TTH per Gram of Cornstarch

Providing greater protection from severe hypoglycemia versus placebo (p-value=0.0269)

Change from Baseline in time (minutes) to hypoglycemia (< 54 mg/dL) per gram of cornstarch in a controlled fasting challenge (CFC)



Phase 3 trial

Patients Treated with DTX401 Reported Moderate to Much Improved PGIC Scores and Support 30% Reduction in Cornstarch as Clinically Meaningful

PGIC at Week 48	Placebo (N=23)	DTX401 (N=19)	p-value
Median Patients Global Impression of Change (PGIC) Score#	+1.0 Minimally Improved	+2.0 Moderately Improved	0.132*
Much Improved (+3.0)	9%	26%	
Worsening to No Change (-3.0 to 0.0)	48%	21%	

PGIC is a 7-point scale ranging from -3 = Much Worse to 3 = Much Improved
* Trial was not designed to have 80% power for this endpoint.

Emerging themes from interviews provide further insight to changes while in the study

- Better glycemic stability
- Improved physical appearance / physical function (ability to play sports/exercise)
- Less restrictive, easier to plan diet
- Improved emotional health (less worry)
- Less fatigue
- Some report blinded CGM made it hard to manage GSDIa (leading to over-compensation on SMBG, worsening control)

Summary: DTX401 showed a persistent efficacy and consistent safety profile in all treated participants for up to five years

- **Significant reductions in cornstarch intake in all participants that have persisted for up to 5 years in Cohort 1 and Cohort 2 participants (phase 1/2 trial)**
- **Time in euglycemia (assessed by CGM) remained stable or improved**
- **Safety profile was similar across all participants treated in all dose cohorts and as expected for DTX401**
- **Fasting TTH outcomes have been positive and clinically meaningful in many participants. Variability in CFCs and hormonal abnormalities at the time of CFC warrant further evaluation**
- **After DTX401 administration, cornstarch dependance was reduced and non-cornstarch carbohydrates, fat, and protein were increased to allow for a more balanced diet**
- **Several GSDIa symptom and impact improvements were reported by patients following treatment. PGIC score improvements correlated with cornstarch reductions**
- **Results from phase 3 trial at week 96 being analyzed**

Grazie!

Per la partecipazione al Convegno e il loro supporto all'Associazione, ringraziamo: **Sanofi Genzyme, Amicus Therapeutics, Dr. Scharr (Kanso), Vitaflo (Mevalia) e SSIEM - Society for the study of inborn errors of metabolism.**

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Per la loro collaborazione e per essere al nostro fianco, ringraziamo:
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