Initial data from the Phase 1/2 clinical study of BEAM-301, an in vivo base editor targeting the R83C variant in glycogen storage disease type Ia (GSDIa)

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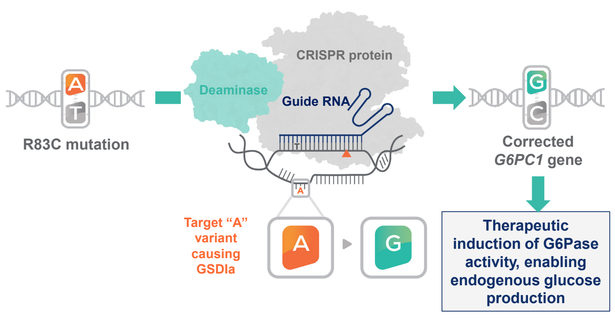
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Introduction

- Glycogen storage disease type Ia (GSDIa) is an autosomal recessive metabolic disease caused by pathogenic variants in the *G6PC1* gene, leading to deficiency or inactivity of the glucose-6-phosphatase enzyme (G6Pase)[1,2]
  - *G6PC1*-c.247C>T (p.R83C) is among the most prevalent pathogenic GSDIa variants, especially in populations experiencing strong ethnic founder mutation effects, and is associated with a severe phenotype that leads to little or no enzymatic activity[2,3]
- Individuals with the R83C mutation cannot release glucose from glycogen or produce glucose de novo, and so require frequent starch administration to prevent hypoglycemia[1]
- GSDIa is associated with life-threatening hypoglycemia, and excess glycogen accumulating in the liver, kidney, and intestines; this causes secondary complications, including metabolic derangements, chronic kidney disease, and hepatic adenomas[1,4]
- Recently, pariglasgene brecaparvovec, an adeno-associated virus-based gene therapy that, as an adjunct therapy, can reduce daily starch intake, received accelerated US regulatory approval[5]
- BEAM-301 is an investigational lipid nanoparticle (LNP)-based therapy containing guide RNA and adenine base editor mRNA, designed to permanently correct the *G6PC1* mutation in hepatocytes via A-to-G editing after a single administration (**Figure 1**)[2]

Figure 1: BEAM-301 mechanism of action[2]



CRISPR, clustered regularly interspaced short palindromic repeats; G6Pase, glucose-6-phosphatase enzyme; G6PC1, glucose-6-phosphatase catalytic subunit 1; GSDIa, glycogen storage disease type Ia; mRNA, messenger RNA

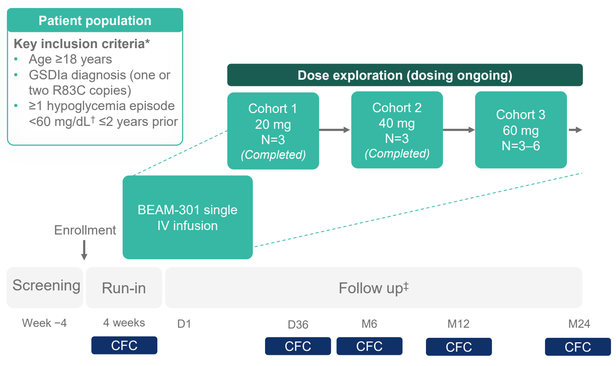
Aim

- The ongoing Phase 1/2, open-label, single-ascending-dose, multicenter BEAM-301 clinical study (NCT06735755) is evaluating the safety and efficacy of BEAM-301 in patients with GSDIa who are homozygous or compound heterozygous for the R83C variant

Methods

- Dosing and cohort information for the dose-exploration stage are shown in the study design (**Figure 2**)

Figure 2: BEAM-301 study design[6]



Key endpoints*

Primary:
- TEAEs, serious TEAEs, and DLTs

Secondary:
- Change from BL in TTH
- Metabolic parameters over time
- Change from BL in starch supplementation‖

Exploratory:
- Change from BL in % of time spent in euglycemia, hypoglycemia, and hyperglycemia (CGM)
- Change from BL in glucose and metabolic parameters during CFCs

*List is not exhaustive; †3.3 mmol/L; ‡only follow-up visits during which patients are hospitalized for CFC are shown; §other criteria include lactate >10 mmol/L, pH <7.25, HCO_3 <15 mmol/L, altered mental status, vomiting, loss of consciousness, OR patient requests to stop; ‖total amount and number of doses per day. BL, baseline; CFC, controlled fasting challenge; CGM, continuous glucose monitoring; D, Day; DLT, dose-limiting toxicity; GSDIa, glycogen storage disease type Ia; IV, intravenous; M, Month; TEAE, treatment-emergent adverse event; TTH, time to fasting hypoglycemia

- Medications administered to mitigate infusion-related reactions (IRRs) include prednisone/prednisolone, H1 and H2 blockers, and acetaminophen
- BEAM-301 infusion time is 2 hours and can be extended at the discretion of the investigator to mitigate any potential IRRs
- Baseline and post-infusion assessments include monitoring for adverse events, controlled fasting challenges (CFCs), continuous glucose monitoring (CGM), and metabolic parameters

Results

Patient disposition and baseline characteristics

- As of data cutoff (August 17, 2026), six patients have received BEAM-301 with a median (range) follow up of 7.6 (1.9–16.6) months
- Three patients each have received BEAM-301 in the 20 mg and 40 mg cohorts (**Table 1**)

Table 1: Baseline demographics and clinical characteristics

	Cohort 1: 20 mg (N=3)	Cohort 2: 40 mg (N=3)	Total (N=6)
Age (years), median (range)	26.0 (26.0–43.0)	42.0 (26.0–50.0)	34.0 (26.0–50.0)
Sex, n (%)			
Male	2 (66.7)	1 (33.3)	3 (50.0)
Female	1 (33.3)	2 (66.7)	3 (50.0)
BMI (kg/m²), median (range)	28.1 (24.3–43.8)	24.6 (22.5–53.4)	26.4 (22.5–53.4)
Genotype, n (%)			
R83C homozygous	2 (66.7)	2 (66.7)	4 (66.7)
R83C compound heterozygous*	1 (33.3)	1 (33.3)	2 (33.3)
TTH (hours), median (range)	2.9 (1.1–3.0)	2.5 (2.3–3.1)	2.7 (1.1–3.1)
Daily starch intake, median (range)			
Total dose (g/day)	315 (248.0–330.0)	255 (236.0–275.0)	265 (236.0–330.0)
Number of doses	6 (6–7)	5 (5–6)	6 (5–7)
Triglyceride (mg/dL), median (range)	260 (130.7–289.7)	237 (202.7–296.0)	248.5 (130.7–296.0)

*All patients had the p.R83C and p.G270V mutation
BMI, body mass index; TTH, time to fasting hypoglycemia

Safety

- BEAM-301 20 mg and 40 mg showed an **acceptable safety profile**, with **no dose-limiting toxicities**, no treatment-emergent adverse event (TEAE)-related discontinuations, and **no Grade 4/5 TEAEs** (**Table 2**)

Table 2: Safety summary

Number of patients with events (%)	Cohort 1: 20 mg (N=3)	Cohort 2: 40 mg (N=3)	Total (N=6)
Any TEAE	3 (100)	3 (100)	6 (100)
Related to BEAM-301	3 (100)	3 (100)	6 (100)
Any TEAE ≥Grade 3*	2 (66.7)	1 (33.3)	3 (50.0)
Related to BEAM-301	2 (66.7)	1 (33.3)	3 (50.0)
Any serious TEAE†	2 (66.7)	2 (66.7)	4 (66.7)
Events			
IRR	2 (66.7)	1 (33.3)	3 (50.0)
Diarrhea	0	1 (33.3)	1 (33.3)
Rhabdomyolysis‡	0	1 (33.3)	1 (33.3)
Serious TEAE related to BEAM-301	2 (66.7)	2 (66.7)	4 (66.7)
Any DLT	0	0	0
Any TEAE leading to death	0	0	0
Any TEAE leading to dose withdrawal	0	0	0
IRR Grade 1 / 2 / 3	1 (33.3) / 1 (33.3) / 2 (66.7)	0 / 1 (33.3) / 1 (33.3)	1 (16.7) / 2 (33.3) / 3 (50.0)
ALT elevation Grade 1 / 2 / 3	2 (66.7) / 0 / 0	2 (66.7) / 0 / 0	4 (66.7) / 0 / 0
AST elevation Grade 1 / 2 / 3	2 (66.7) / 0 / 0	1 (33.3) / 1 (33.3) / 0	3 (50.0) / 1 (16.7) / 0

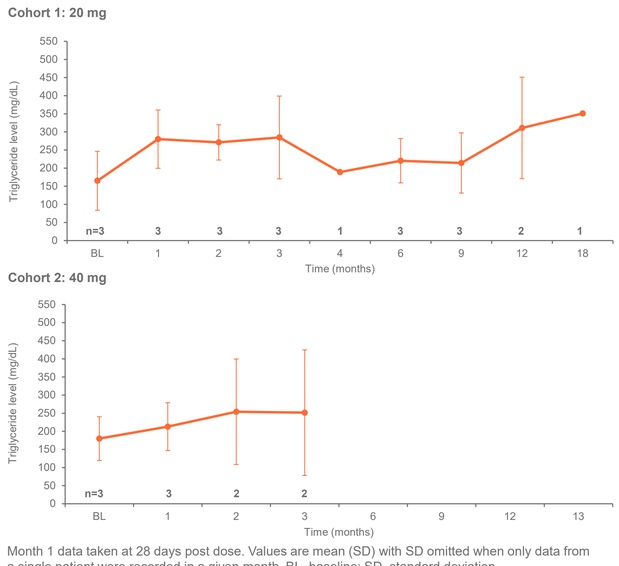
*No Grade 4 or 5 TEAEs have been reported; †all serious TEAEs have resolved; ‡occurred in a patient who also had an IRR, with bilateral calf involvement, peak creatine kinase <1,000 U/L, and no renal involvement. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event

- IRRs and transient transaminase elevations were the most frequent treatment-related TEAEs, consistent with the known safety profile of intravenous (IV) LNPs
  - IRRs occurred in 5/6 patients, comprising three serious Grade 3 and three nonserious (two Grade 2, one Grade 1) events; all resolved with or without treatment
  - Use of shorter-acting, lower-potency corticosteroids may have contributed to IRR severity; premedication and infusion rate regimens have been modified
  - Transaminase elevations were primarily Grade 1, transient, and resolved without intervention; patients remained asymptomatic and total bilirubin remained within normal limits

Triglyceride levels

- At the last evaluable timepoint, triglyceride levels were generally comparable to those at baseline (**Figure 3**)

Figure 3: Post-treatment triglyceride levels over time per dose cohort

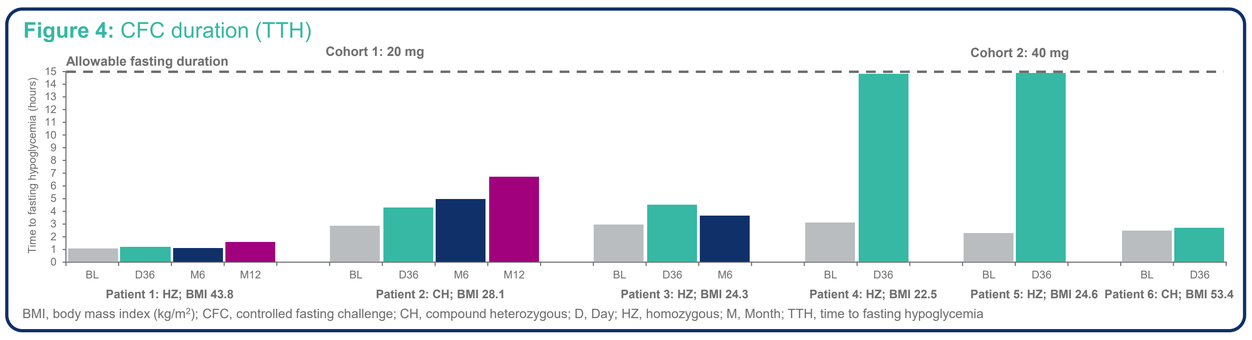


Month 1 data taken at 28 days post dose. Values are mean (SD) with SD omitted when only data from a single patient were recorded in a given month. BL, baseline; SD, standard deviation

Time to fasting hypoglycemia (TTH) during controlled fasting challenges (CFCs)

- Median (range) TTH increased from 2.9 (1.1–3.0) hours at baseline to 4.3 (1.3–4.6) hours at Day 36 in the 20 mg cohort, and from 2.5 (2.3–3.1) hours to 15.0 (2.8–15.0) hours in the 40 mg cohort (**Figure 4**)
- In the 40 mg cohort, **two of three patients achieved the protocol-defined maximum CFC duration (TTH) of 15 hours**, consistent with restored endogenous glucose production (**Figure 4**)

Figure 4: CFC duration (TTH)

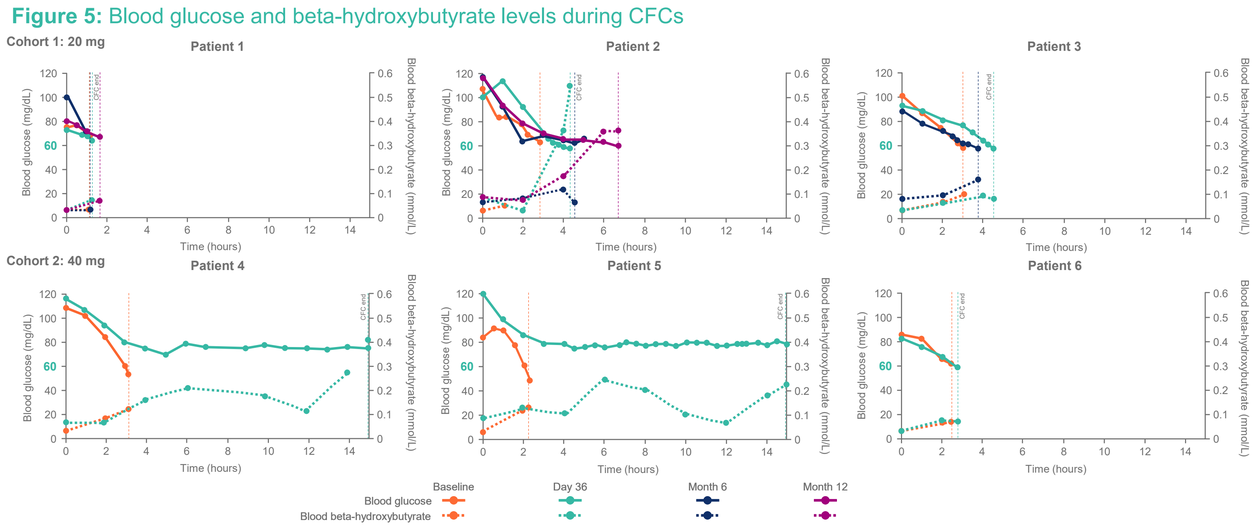


BMI, body mass index (kg/m²); CFC, controlled fasting challenge; CH, compound heterozygous; D, Day; HZ, homozygous; M, Month; TTH, time to fasting hypoglycemia

Blood glucose and metabolites during CFCs

- Two patients had CFCs lasting the maximum of 15 hours, with glucose ≥60 mg/dL and the accompanying metabolic parameters consistent with induction of G6Pase activity (**Figure 5**)
  - Blood glucose levels were stable in the euglycemic range, with increases in beta-hydroxybutyrate levels
  - During CFC, lactate levels did not demonstrate the marked increase that is expected in the GSDIa patient population (1.0–3.5 mmol/L; data not shown)
- Increased beta-hydroxybutyrate levels were also observed intermittently post-treatment in some patients who received 20 mg BEAM-301; all six patients had hypoketotic hypoglycemia at baseline as expected (**Figure 5**)

Figure 5: Blood glucose and beta-hydroxybutyrate levels during CFCs

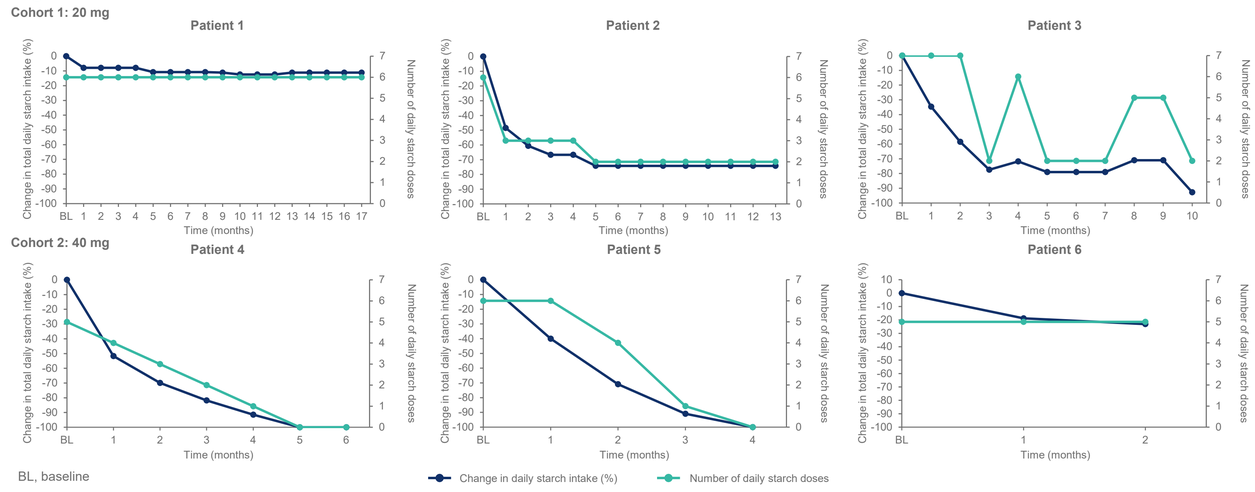


Blood glucose 60 mg/dL = 3.3 mmol/L; 120 mg/dL = 6.7 mmol/L. CFC, controlled fasting challenge

Daily starch intake and daily number of starch doses generally decreased post BEAM-301

- **Two of three patients in the 40 mg cohort no longer required any supplementation** (**Figure 6**)

Figure 6: Post-treatment prescribed starch supplementation over time

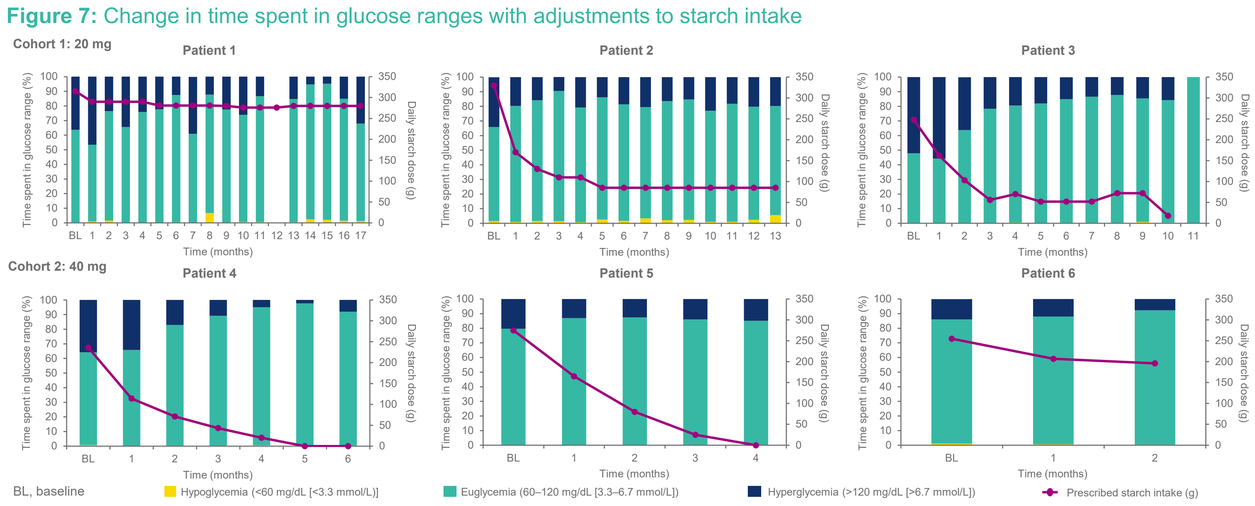


BL, baseline

Time in hypoglycemic range did not increase despite general reductions in starch intake

- Continuous glucose monitoring demonstrated increased time in euglycemic, and less time in hyperglycemic, glucose range post BEAM-301 (**Figure 7**)

Figure 7: Change in time spent in glucose ranges with adjustments to starch intake



BL, baseline

Conclusions

Initial data from the BEAM-301 study demonstrate an acceptable safety profile and suggest induction of G6Pase activity in patients with GSDIa:

- Safety profile across 20 mg and 40 mg doses that is consistent with known risks associated with IV LNP administration
- Evidence of significant endogenous glucose production in GSDIa after single-dose administration
- Two of three patients in the 40 mg cohort reaching the 15-hour fasting maximum, accompanied by a 100% reduction in daily starch intake (ie, freedom from any starch supplementation)
- No overall increase in time spent in hypoglycemia despite reduction in daily starch intake

Based on these results, patients are now being recruited into the **60 mg** dose cohort

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Disclosure

Dr. Riba-Wolman is a site Principal Investigator for clinical trials with Ultragenyx Pharmaceutical, Inc. and Beam Therapeutics, Inc.

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