Robust HbF induction and improvement of anemia and hemolysis with base editing in sickle cell disease: safety and efficacy findings from the ongoing BEACON study

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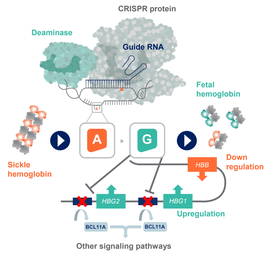
Introduction

- Sickle cell disease (SCD) is a heterogeneous autosomal recessive blood disorder characterized by abnormal sickle hemoglobin (HbS) production and leads to chronic hemolytic anemia and recurrent severe vaso-occlusive crises (sVOCs)[1,2]
- BEAM-101 is an investigational cell therapy comprising base-edited autologous CD34+ hematopoietic stem and progenitor cells (HSPC) that target *HBG1/2* promoters and inhibit BCL11A binding without altering BCL11A expression, resulting in a switch in hemoglobin (Hb) production from HbS to anti-sickling fetal Hb (HbF) (**Figure 1**)
- We present updated data from BEACON (NCT05456880), a Phase 1/2, single-arm, open-label study evaluating the safety and efficacy of a single dose of BEAM-101 in patients with SCD and recurrent sVOCs

Figure 1: BEAM-101 mechanism of action



A, adenine; BCL11A, transcription factor B-cell lymphoma/leukemia 11A; CRISPR, clustered regularly interspaced short palindromic repeats; G, guanine; HBB, hemoglobin subunit beta; HBG, hemoglobin subunit gamma; RNA, ribonucleic acid

Methods

Figure 2: BEACON is a Phase 1/2 study evaluating the safety and efficacy of BEAM-101 in patients with SCD and sVOCs[3]

Key eligibility criteria	Key safety endpoints	Key efficacy endpoints
▶ Age ≥12 to ≤35 years ▶ SCD with β^S/β^S, β^S/β^0, or β^S/β^+ genotypes ▶ ≥4 sVOCs in 2 years prior to screening ▶ No available matched sibling donor ▶ No history of overt stroke	▶ Proportion of patients with successful neutrophil engraftment ▶ Time to neutrophil engraftment ▶ Time to platelet engraftment	▶ Proportion of patients sVOC-free for 12 consecutive months* ▶ Total Hb levels ▶ HbF and HbS levels ▶ Hemolysis parameters ▶ RBC function and organ damage ▶ Bone marrow and peripheral blood editing

Study enrollment is complete

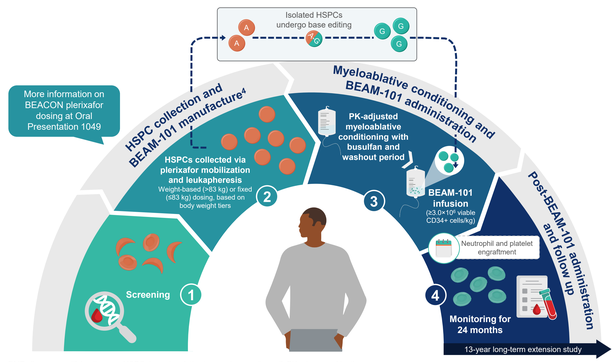
Phase 1/2, non-randomized, open-label, single-arm, multicenter, safety and efficacy study of the administration of BEAM-101 to patients with SCD (NCT05456880)

sVOCs were defined as acute pain crises in individuals with SCD, with no medically determined cause other than a VOC that required ≥24 hours' management in a hospital or observation unit, or a visit to an emergency department, urgent care, or outpatient facility involving therapy with an opioid or an intravenous or intramuscular nonsteroidal anti-inflammatory drug

*From 60 days after last RBC transfusion

Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease; sVOC, severe vaso-occlusive crisis

Figure 3: The BEACON study involves four key stages



DMT, disease-modifying therapy; HSPC, hematopoietic stem and progenitor cell; PK, pharmacokinetic

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Results

Baseline characteristics

- Safety and efficacy data are available for 31 patients aged 16–34 years (**Tables 1–4**)
- As of August 6, 2025, mean follow up was 6.6 (range, 0.3–20.4) months

Table 1: Baseline demographics and characteristics of patients treated with BEAM-101

Baseline characteristics	N=31
Age (years), mean (range)	22.8 (16–34)
Sex, n (%)	
Male	16 (51.6)
Female	15 (48.4)
Genotype, n (%)	
β^S/β^S	28 (90.3)
β^S/β^0	1 (3.2)
β^S/β^+	2 (6.5)
Race, n (%)	
Black or African American	25 (80.6)
White	1 (3.2)
Not reported	4 (12.9)
Other	1 (3.2)
Previous hydroxyurea use, n (%)	31 (100)
Investigator-reported sVOCs in the 2 years prior to start of study, median (range)	7 (4–60)

All-enrolled population n=54 (43 adults, 11 adolescents)
- 1 discontinued prior to mobilization
  - PI decision
  - 3 not yet started mobilization

Started mobilization n=50 (42 adults, 8 adolescents)
- 2 discontinued prior to dosing
  - 1 mobilization failure
  - 1 PI decision
- 17 not yet dosed

All-treated population Dosed with BEAM-101 n=31 (30 adults, 1 adolescent)
- 1 death 4 months post-infusion
- 1 withdrew consent 5 months post-infusion

Study ongoing

PI, principal investigator; sVOC, severe vaso-occlusive crisis

Mobilization and Stem Cell Collection

- A low number of stem cell collection cycles were needed to manufacture BEAM-101
- Patients required a median of 1 (1–5*) stem cell collection cycle
- A median of 3 (1–13) total collection days was required for BEAM-101 manufacture and storage of back-up/rescue cells

*One patient required a fifth cycle (1 day) to collect rescue/back-up cells at site

- Patients achieved rapid and robust bone marrow reconstitution, with time to neutrophil engraftment at a median of 17.5 (12–30) days with 7 (1–17) neutropenic days
- Platelet engraftment was achieved at a median of 19 (11–53) days. Nine patients did not require a platelet transfusion, of which six had platelet counts that did not drop below 50,000/μL

Table 2: BEAM-101 treatment and engraftment characteristics

Treatment	N=31
Estimated average AUC of busulfan for entire conditioning (μg*h/mL), mean (range)	71 (61.0–86.1)
BEAM-101 dose infused (×10⁶ CD34+ cells/kg), mean (range)	6.2 (3.2–23.4)
Duration (months) of follow up after BEAM-101 dosing, mean (range)	6.6 (0.3–20.4)
Day of last RBC transfusion, median (range)	14 (1–26)*
Neutrophil engraftment	**N=28†**
Time to neutrophil engraftment (days), median (range)	17.5 (12–30)
Duration of severe neutropenia (ANC <500 cells/μL) (days), median (range)	7 (1–17)
Platelet engraftment	**N=27‡**
Time to platelet engraftment (days), median (range)	19 (11–53)
Did not require a platelet transfusion, n (%)	9 (29)
Platelet count remained ≥50,000/μL, n (%)	6 (19.4)

*One patient was excluded who required several RBC transfusions up to 122 days due to acute illness that ultimately resulted in death at four months post-infusion
†Three patients achieved neutrophil engraftment after the data cutoff date at 17, 17, and 21 days post-BEAM-101 infusion
‡Four patients achieved platelet engraftment after the data cutoff date at 24, 24, 26, and 52 days post-BEAM-101 infusion
ANC, absolute neutrophil count; AUC, area under curve; RBC, red blood cell

The safety profile of BEAM-101's treatment regimen is consistent with busulfan conditioning, autologous HSCT, and underlying SCD

Table 3: Summary of TEAEs

Patients with, n (%)	N=31
Any TEAEs	31 (100)
Related to BEAM-101	3 (9.7)*
Any TEAEs ≥ Grade 3	27 (87.1)
Related to BEAM-101	1 (3.2)†
Serious TEAEs	12 (38.7)
Related to BEAM-101	0
Death	1 (4)‡
Related to BEAM-101	0

*Included cough, vomiting, dyspnea (1 patient); muscle spasms, facial swelling (1 patient); and dizziness (1 patient); all Day 1 events, excluding muscle spasms and facial swelling
†All related TEAEs were Grade ≤2 except one non-serious Grade 3 allergic facial swelling 11 weeks post-infusion that resolved the same day and was assessed as possibly related to BEAM-101 by investigator
‡One patient died 4 months post-BEAM-101 infusion, likely related to idiopathic pneumonia syndrome secondary to busulfan conditioning and unrelated to BEAM-101 as previously reported
HSCT, hematopoietic stem cell transplantation; SCD, sickle cell disease; TEAE, treatment-emergent adverse event

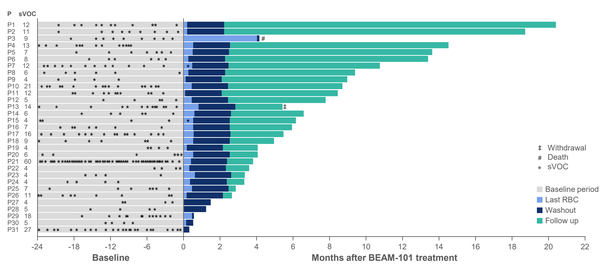
Table 4: Most common TEAEs

Most common TEAEs , n (%)	N=31
Stomatitis	24 (77.4)
Febrile neutropenia	22 (71.0)
Decreased appetite	10 (32.3)
Hypokalemia	10 (32.3)
Skin hyperpigmentation	10 (32.3)
Platelet count decreased	8 (25.8)
Anemia	7 (22.6)
Hypomagnesemia	7 (22.6)
Constipation	6 (19.4)
Hypertension	6 (19.4)
Nausea	6 (19.4)
Anxiety	5 (16.1)
Headache	5 (16.1)
Peripheral edema	5 (16.1)
Pruritus	5 (16.1)
Pyrexia	5 (16.1)

TEAE, treatment-emergent adverse event

Incidence of investigator-reported sVOCs following BEAM-101 treatment

Figure 4: No investigator-reported sVOCs post-engraftment

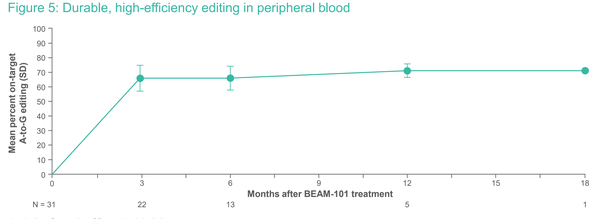


Investigator-reported sVOCs in this figure have not been formally adjudicated
P, patient; RBC, red blood cell; sVOC, severe vaso-occlusive crisis

Editing characteristics

- Mean bone marrow editing was 76.8% by 12 months (n=4)

Figure 5: Durable, high-efficiency editing in peripheral blood

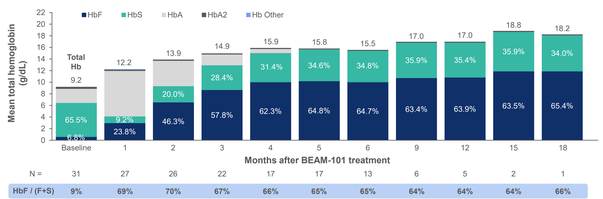


A, adenine; G, guanine; SD, standard deviation

Hemoglobin and other blood analyses

- Rapid and robust HbF induction was seen with mean endogenous HbF (HbF/[HbF+HbS]) >60% and HbS <40% in non-transfused blood by Month 1 that was sustained through follow up (**Figure 6**)
- Elevated total Hb levels above the upper limit of normal were observed in four patients beyond Month 6 without any associated clinical manifestations or therapeutic interventions needed

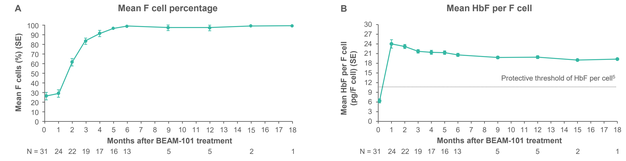
Figure 6: Changes in mean total Hb, HbF, and HbS levels



HbF % is calculated as a % of untransfused blood (HbF/HbF+HbS)
Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin

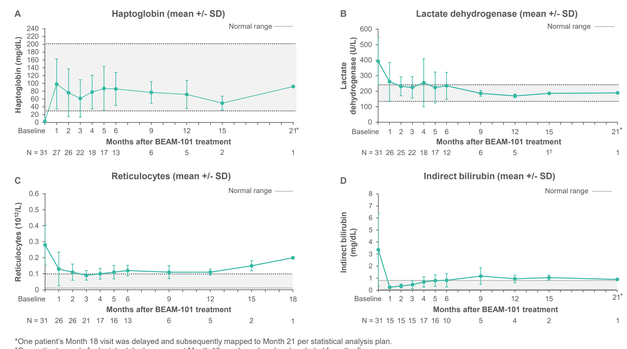
- In total peripheral blood at Month 6, mean % HbF-containing (F cells) was 99.3% (range, 97.0–99.9) with a mean of 20.6 pg HbF/F cell, well above the protective threshold against sickling (**Figure 7**)

Figure 7: Pancellular and high levels of HbF per cell were observed post-BEAM-101



F cell, HbF-containing cell; HbF, fetal hemoglobin; SE, standard error

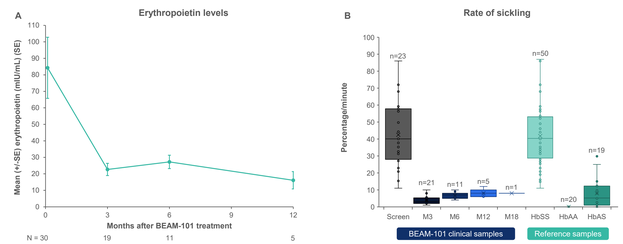
Figure 8: Markers of hemolysis normalized or improved post-BEAM-101



*One patient's Month 18 visit was delayed and subsequently mapped to Month 21 per statistical analysis plan.
†One patient sample for lactate dehydrogenase at Month 15 was hemolyzed and excluded from the figure.
SD, standard deviation

- Elevated baseline erythropoietin levels trended toward normal post-BEAM-101, indicating reduced hypoxic drive (**Figure 9A**)
- Rate of sickling was captured using the dynamic sickling assay[6] and decreased to levels comparable with sickle cell trait reference samples post-BEAM-101 (**Figure 9B**)

Figure 9: Evidence of improved RBC health and function post-BEAM-101



HbAA, normal hemoglobin; HbAS, sickle cell trait; HbSS, sickle cell disease; M, month; RBC, red blood cell; SE, standard error

Conclusions

- BEAM-101's automated, closed, and wholly owned manufacturing process ensured **robust CD34+ cell yield** and **high editing efficiency** with **no manufacturing failures**
- Patients required a **low number of stem cell collection cycles** and achieved **rapid engraftment**, potentially leading to enhanced safety of the BEAM-101 treatment regimen and reduction in treatment burden
- The safety profile of BEAM-101's treatment regimen was **consistent** with busulfan conditioning, autologous HSCT, and underlying SCD
- **No severe VOCs** were reported by investigators post-engraftment
- Treatment with BEAM-101 resulted in **substantial reduction in HbS <40%** through **rapid and robust pancellular production of anti-sickling HbF >60%**
- Improvement or resolution of anemia, hemolysis, elevated erythropoietin, and sickling in all patients suggests **recovery of normal red blood cell (RBC) health and function**
- Novel base editing with BEAM-101 offers a **one-time potentially transformative therapy** as an option for patients with SCD that may **decrease treatment burden** for patients, families, and healthcare facilities