Base editing for sickle cell disease: ongoing results from the BEACON study evaluating the safety and efficacy of BEAM-101, the first base-edited autologous CD34+ HSPC one-time cell therapy

Contact Info:
clinicalinfo@beamtx.com

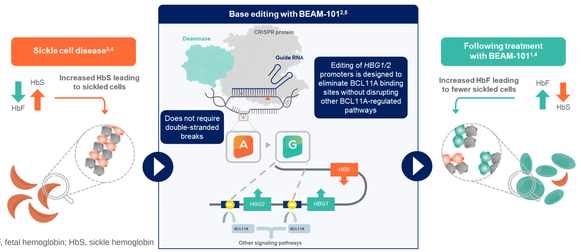
Ashish O Gupta,[1] Akshay Sharma,[2] Jignesh Dalal,[3] Julie Kanter,[4] Ernesto Ayala,[5] John F DiPersio,[6] Haydar Frangoul,[7] Markus Mapara,[8] Jennifer J Jaroscak,[9] Asif Alavi,[10] Mary Eapen,[11] Stacey Rifkin-Zenenberg,[12] Edward D Ziga,[13] Elizabeth Stenger,[14] Rabi Hanna,[15] Tami D John,[16] Shanna White,[17] Thomas S Bowman,[18] Yinzhong Chen,[18] Sarah Chesler,[18] Priya S Chockalingam,[18] Ling Lin,[18] John J Ko,[18] Marcelyne Joseney-Antoine,[18] Leanne Ianniello,[18] Guo Chen,[18] Beth Gardner,[18] Sunita Goyal,[18] Amy Simon,[18] Alexis A Thompson,[19] Matthew M Heeney[20]

[1]Division of Pediatric Blood and Marrow Transplant and Cellular Therapies, University of Minnesota, Minneapolis, MN, USA; [2]Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, TN, USA; [3]Division of Hematology and Bone Marrow Transplant, Rainbow Babies & Children's Hospital, Cleveland, OH, USA; [4]Division of Hematology and Oncology, University of Alabama at Birmingham, AL, USA; [5]Department of Hematology/Oncology, Mayo Clinic, Jacksonville, FL, USA; [6]Division of Oncology, Washington University, St. Louis, MO; [7]Sarah Cannon Research Institute at TriStar Centennial Children's Hospital, Nashville, TN, USA; [8]Ossium Health, San Francisco, CA, USA; [9]Medical University of South Carolina, Charleston, SC, USA; [10]Henry Ford Health System, Detroit, MI, USA; [11]Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [12]Pediatric Hematology/Oncology Division, Hackensack University Medical Center, Hackensack, NJ, USA; [13]Miller School of Medicine, Miami, FL, USA; [14]Aflac Cancer & Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA; [15]Cleveland Clinic Children's Hospital, Cleveland, OH, USA; [16]Stanford University, Palo Alto, CA, USA; [17]Phoenix Children's Hospital, Phoenix, AZ, USA; [18]Beam Therapeutics Inc., Cambridge, MA, USA; [19]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [20]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA

Introduction

- Individuals with sickle cell disease (SCD) with elevated levels of anti-sickling fetal hemoglobin (HbF) have attenuated disease manifestations[1]
- BEAM-101 is an investigational cell therapy consisting of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) that are base edited ex vivo to mimic naturally occurring A-to-G substitutions in the promoters of the *HBG1/2* genes, disrupting BCL11A transcriptional repressor binding sites, leading to upregulation of HbF (**Figure 1**)[2]

Figure 1: BEAM-101 uses precise base editing to increase levels of HbF



HbF, fetal hemoglobin; HbS, sickle hemoglobin

Aim

- 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 (pts) with SCD and frequent and severe vaso-occlusive crises (sVOCs)

Methods

- Key eligibility criteria and key safety and efficacy endpoints are shown in **Figure 2**

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

Key eligibility criteria
- Age ≥12 to ≤35 years
- SCD with β^S/β^S, β^S/β^0, or β^S/β^+ genotypes
- ≥4 sVOCs in 24 months prior to screening
- No available matched sibling donor
- No history of overt stroke

Key safety endpoints
- Proportion of patients with successful neutrophil engraftment
- Time to neutrophil engraftment
- Time to platelet engraftment

Key efficacy endpoints
- Proportion of patients sVOC-free for 12 consecutive months*
- Proportion of patients who were hospitalization-free for sVOCs for at least 12 months*
- Total Hb levels
- HbF and HbS levels
- Hemolysis parameters
- RBC function and organ damage

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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). To qualify as a sVOC, the event must consist of acute episodes of pain, with no medically determined cause other than a VOC that required at least 24 hours of 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 IV or IM NSAID; or ACS, as defined by the acute onset of pneumonia-like symptoms (e.g., cough, fever, shortness of breath) along with new pulmonary infiltrates; or splenic sequestration crisis, as defined by left upper quadrant pain, splenic enlargement, and a decrease in Hb of ≥2 g/dL; or priapism episode, defined as a sustained, unwanted, painful erection requiring evaluation and treatment at a medical facility. *From 60 days after last RBC transfusion. ACS, acute chest syndrome; Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; IM, intramuscular; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug; RBC, red blood cell; SCD, sickle cell disease; sVOC, severe vaso-occlusive crisis

- For peripheral cell collection, plerixafor dosing was weight-based (>83 kg) or fixed dose (≤83 kg), based on body weight tiers
- After mobilization with plerixafor, autologous CD34+ HSPCs were collected by leukapheresis and genetically modified with an adenine base editor[2]
- Following myeloablative conditioning with pharmacokinetically adjusted busulfan, patients received a single infusion of BEAM-101 (≥3.0×10^6 viable CD34+ cells/kg)[2]
- Patients were monitored for neutrophil and platelet engraftment in an inpatient setting until neutrophil engraftment; they were further monitored as outpatients until Month 24 post-treatment[2]
- The primary efficacy endpoint was the proportion of patients free of adjudicated sVOCs for 12 consecutive months[2]

References

1. Steinberg MH et al. Blood 2014;123:481–485
2. Beam Therapeutics Inc. Protocol BTX-AUT-001
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4. Akinsheye I et al. Blood 2011;118:19–27
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Acknowledgments

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Results

Baseline, treatment, and engraftment characteristics

- Safety and efficacy data are available for N=17 patients, aged 18–34 years (**Tables 1–4**)
- At data cutoff (Feb 28, 2025), median (range) follow up was 3.7 (0.2–15.1) months
- Patients required a median of one mobilization cycle (range: 1–3)
  - 11 patients (64.7%) required only one mobilization cycle, four patients (23.5%) required two cycles, and two patients (11.8%) required three cycles
  - A median (range) of 3 (2–11) total mobilization days was required for drug product manufacture
- Patients had rapid neutrophil and platelet engraftment with few days of severe neutropenia
- Of the 16 patients who achieved neutrophil engraftment by the datacut, median time to neutrophil engraftment was 16.5 (12–30) days, with a median of 7.0 (4–17) days of severe neutropenia. One patient achieved neutrophil engraftment post-datacut on Day 19 (**Table 2**)
- Of the 14 patients who achieved platelet engraftment by the datacut, median time to platelet engraftment was 19.5 (11–34) days. The other three patients achieved platelet engraftment post-datacut on Day 27, 28, and 50 **(Table 2)**

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

Baseline characteristics	N=17
Age (years), mean (range)	22.9 (18–34)
Sex, n (%)	
Male	10 (58.8)
Female	7 (41.2)
Genotype, n (%)	
β^S/β^S	16 (94.1)
β^S/β^0	1 (5.9)
Race, n (%)	
Black or African American	15 (88.2)
Previous hydroxyurea use, n (%)*	10 (58.8)
Investigator-reported sVOCs in the 2 years prior to start of study, median (range)	9 (4–18)

Data cutoff Feb 28, 2025. *Taking at screening. sVOC, severe vaso-occlusive crisis

Table 2: BEAM-101 treatment and engraftment characteristics

Treatment	N=17
Number of mobilization and apheresis cycles, median (range)	1 (1–3)
Estimated average AUC of busulfan for entire conditioning (μg*h/mL), mean (range)*	70.5 (50.2–89.2)
BEAM-101 dose infused (×10^6 CD34+ cells/kg), mean (range)	7.9 (3.2–23.4)
Duration (months) of follow up after BEAM-101 dosing, median (range)	3.7 (0.2–15.1)
Day of last RBC transfusion, median (range)	15 (1–122†)
Neutrophil engraftment‡	**N=16**
Achieved neutrophil count ANC ≥500 cells/μL for 3 consecutive days, n (%)	16 (100)
Time to neutrophil engraftment (days), median (range)	16.5 (12–30)
Duration of severe neutropenia (ANC <500 cells/μL) (days), median (range)	7.0 (4–17)
Platelet engraftment‡¶	**N=14**
Achieved platelet count ≥50,000/μL on 3 separate days, n (%)§	14 (100)
Time to platelet engraftment (days), median (range)	19.5 (11–34)
Did not require a platelet transfusion, n (%)	7 (50)
Number of patients who did not have a drop in platelet count below 50K, and without platelet transfusion	3 (21.4%)

Data cutoff Feb 28, 2025. Therapeutic drug monitoring for busulfan was performed and dosing was adjusted based upon plasma busulfan concentrations to maintain a daily target busulfan AUC of 20 μg*h/mL with a cumulative AUC target of 80 μg*h/mL. Neutrophil engraftment defined as ANC ≥500 cells/μL for 3 consecutive days independent of growth factor support. Platelet engraftment defined as post-nadir platelet count ≥50,000/μL on 3 separate days without receiving a platelet transfusion for at least 7 days prior to the first of the three measurements through to the last measurement. *n=14; AUC could not be calculated for the remaining three patients as busulfan pharmacokinetic data were incomplete; †one patient required blood transfusions up to Day 122 as part of ongoing management of critical illness; excluding this patient, the range of last day of RBC transfusion is 1–26 days; ‡at the time of datacut; one patient achieved neutrophil engraftment post-datacut on Day 19; §at the time of datacut; three patients achieved platelet engraftment post-datacut on Day 27, 28, and 50; ¶four patients experienced ≥Grade 4 thrombocytopenia; ‖three patients' platelets did not drop below 50,000/μL and did not have any platelet transfusions. ANC, absolute neutrophil count; AUC, area under the curve; RBC, red blood cell

BEAM-101 ongoing safety data are consistent with busulfan conditioning, autologous hematopoietic stem cell transplant (HSCT), and underlying SCD

Table 3: Summary of TEAEs

Patients with, n (%)	N=17
Any TEAEs	17 (100)
Related to BEAM-101*	1 (5.9)
Any TEAEs ≥Grade 3	15 (88.2)
Related to BEAM-101*	0
AEs leading to discontinuation	0
Serious TEAEs†	6 (35.3)
Related to BEAM-101	0
Death‡	1 (5.9)
Related to BEAM-101	0

Data cutoff Feb 28, 2025. Related events include events where investigator has assessed relationship as possibly or definitely related to BEAM-101. *After the datacut, the number of patients with related TEAEs was one (non-serious Grade 1 dizziness), and the number of patients with ≥Grade 3 related TEAEs was zero, following site data clarification; †serious TEAEs included sickle cell anemia with crisis, retinal hemorrhage, nausea, device-related infection, septic shock, vascular access complication, acute kidney injury, urinary retention, pneumomediastinum, pulmonary fibrosis, and respiratory failure; ‡one patient died due to respiratory failure, likely related to busulfan conditioning, 4 months after infusion. AE, adverse event; TEAE, treatment-emergent adverse event

Table 4: Most common TEAEs

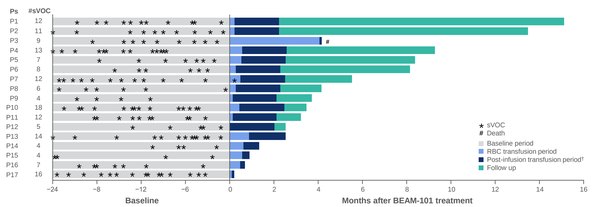
TEAE (≥3 patients), n (%)	N=17
Stomatitis*	12 (70.6)
Febrile neutropenia*	11 (64.7)
Skin hyperpigmentation	5 (29.4)
Decreased appetite*	5 (29.4)
Hypokalemia	5 (29.4)
Anemia*	4 (23.5)
Constipation	4 (23.5)
Headache	4 (23.5)
Hypertension	4 (23.5)
Platelet count decreased	4 (23.5)
Hypervolemia	3 (17.6)
Hypomagnesemia	3 (17.6)
Nausea	3 (17.6)
Edema (peripheral)	3 (17.6)
Pharyngeal inflammation	3 (17.6)
White blood cell count decreased	3 (17.6)

Data cutoff Feb 28, 2025. *Includes events that were ≥Grade 3 in at least three patients. TEAE, treatment-emergent adverse event

Efficacy

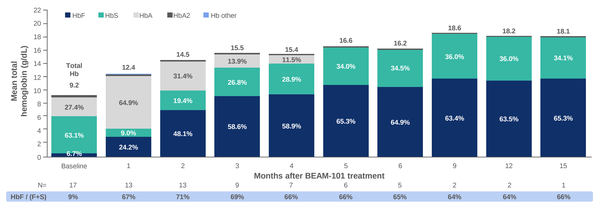
- No patients have experienced any VOCs post-engraftment

Figure 3: Investigator-reported VOCs following treatment with BEAM-101



†60 days post last RBC transfusion. Investigator-reported VOCs reported in this figure have not been formally adjudicated. P, patient; RBC, red blood cell; (s)VOC, (severe) vaso-occlusive crisis

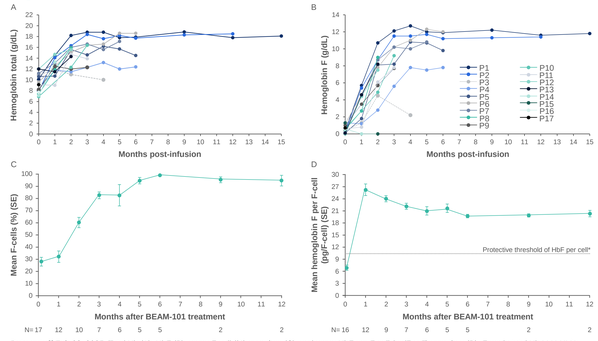
Figure 4: Patients achieved rapid and robust HbF induction with corresponding HbS reduction



Data cutoff Feb 28, 2025. Female total Hb LLN-ULN: 11.5–15 g/dL; male LLN-ULN: 13–17 g/dL. HbF % is calculated as a % of untransfused blood (HbF/HbF+HbS). Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; LLN, lower limit of normal; ULN, upper limit of normal

- Rapid and robust increase in total Hb (**Figure 5A**) and HbF (>60%, **Figure 5B**); both were durable through follow up
- Pancellular HbF expression was observed following elimination of transfused blood (**Figure 5C**)
- Mean HbF (pg/cell) reached the protective threshold[1] by Month 1 and was sustained through follow up (**Figure 5D**)

Figure 5: Total Hb, HbF, and HbF distribution



Data cutoff Feb 28, 2025. Total Hb (A), HbF (B), mean F-cell (%) over time (C), and mean HbF per F-cell (pg/F-cell) over time (D). Female total Hb LLN-ULN: 11.5-15 g/dL; male LLN-ULN: 13-17 g/dL. *Defined as the level of HbF that inhibits deoxyHbS polymerization.[1] F, female; F-cell, HbF-containing cell; Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; LLN, lower limit of normal; M, male; P, patient; SE, standard error; ULN, upper limit of normal

- Decreased erythropoietin following treatment indicates improvements in systemic oxygen delivery (**Figure 6**)
- HbF has a high affinity for oxygen and binds oxygen more readily, especially at lower oxygen tension compared with HbA

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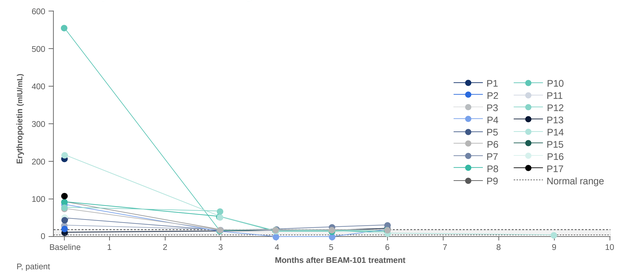
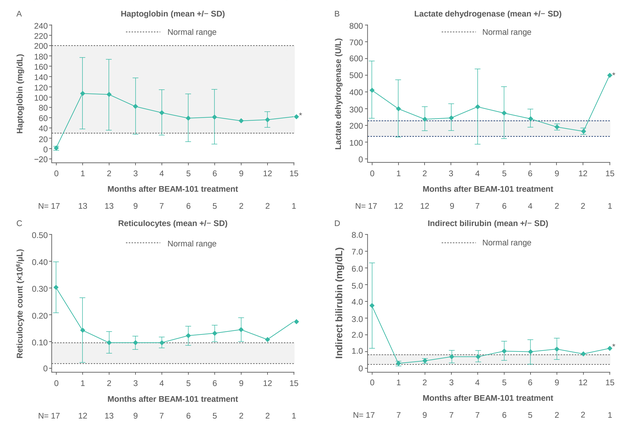
Figure 6: Erythropoietin following treatment with BEAM-101



P, patient

- Hemolysis markers normalized or improved following BEAM-101 treatment (**Figure 7**)

Figure 7: Hemolysis markers following treatment with BEAM-101



*The sample for Month 15 data point was hemolyzed; impacts of hemolysis on assay outcomes should be considered when interpreting results. SD, standard deviation

Conclusions

Safety data from the BEACON study support continuation of the trial and demonstrate robust and sustained increases in HbF expression and resolution of anemia in patients with SCD

- BEAM-101's efficient **collection and manufacturing process** resulted in patients requiring a **median of one mobilization cycle**

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- Patients achieved **rapid neutrophil and platelet engraftment** with low numbers of neutropenic and thrombocytopenic days
- **Ongoing safety data with BEAM-101 are consistent** with busulfan conditioning, autologous HSCT, and underlying SCD
- **No VOCs were reported** by investigators post-engraftment
- All patients achieved **rapid and robust increases in total Hb and HbF (>60%)**; **pancellular** distribution of HbF was **maintained, with HbF/F-cell maintained above protective threshold** through follow up
- All patients achieved **rapid and robust decrease in HbS (<40%) with resolution of anemia**, and markers of hemolysis were **normalized or improved** in all patients

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