INITIAL RESULTS FROM THE BEACON CLINICAL STUDY

A Phase 1/2 study evaluating the safety and efficacy of a single dose of autologous CD34+ base-edited hematopoietic stem cells (BEAM-101) in patients with sickle cell disease with severe vaso-occlusive crises

66th ASH 2024

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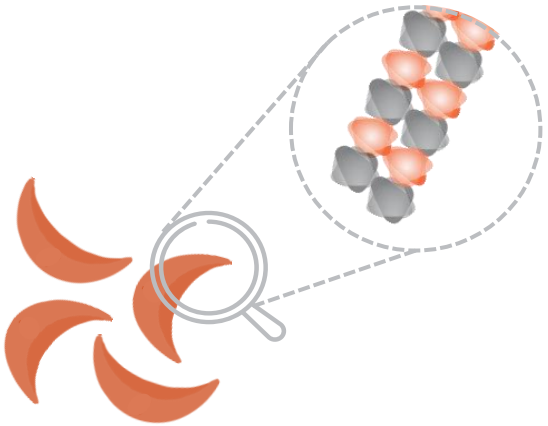
BEAM-101 uses precise base editing to increase levels of HbF

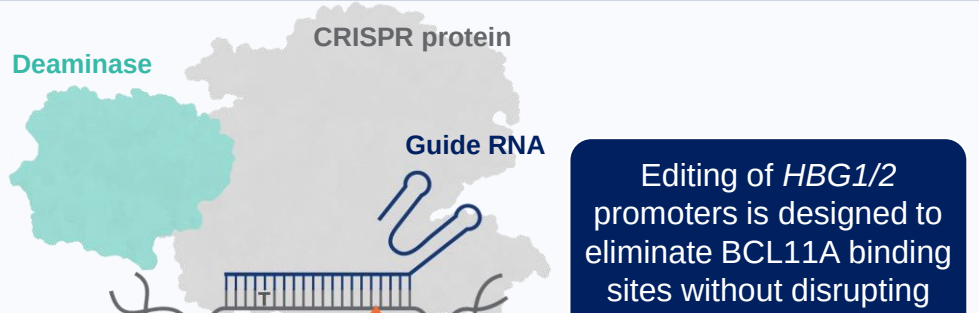
Sickle cell disease[1,2]

HbS ↓ ↑ HbF

Increased HbS leading to sickled cells

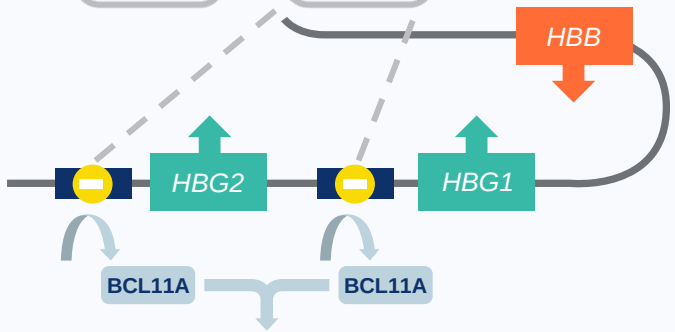


Base editing with BEAM-101[3,4]



Editing of *HBG1/2* promoters is designed to eliminate BCL11A binding sites without disrupting other BCL11A-regulated pathways

Does not require double-stranded breaks

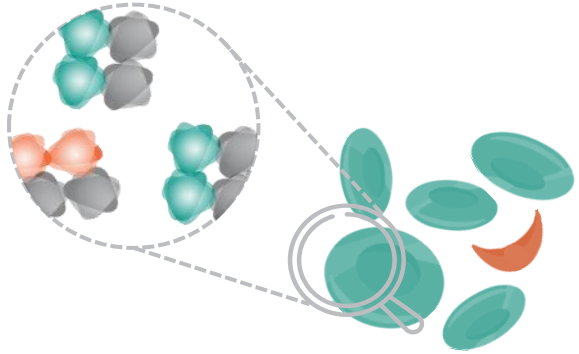


Other signaling pathways

Following treatment with BEAM-101[2,5]

Increased HbF leading to fewer sickled cells

HbF ↑ ↓ HbS



1. Eaton WA, Bunn HF. Blood 2017;129:2719–2726; 2. Akinsheye I, et al. Blood 2011;118:19–27; 3. Beam Therapeutics Inc. Protocol BTX-AUT-001; 4. Beam Therapeutics Inc. Investigator's brochure; 5. Steinberg MH, et al. Blood 2014;123:481–485. 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; HbF, fetal hemoglobin; HbS, sickle hemoglobin; RNA, ribonucleic acid

BEACON is a Phase 1/2 study evaluating safety and efficacy of BEAM-101 in patients with SCD and severe VOCs

Sentinel cohort (N=3)

- ✓Staggered start with SRC review in between
- ✓Enrollment complete
- ✓Dosing complete

DMC review

Expansion cohort

- ✓35+ patients cleared screening and enrolled
- ✓11 patients dosed with the remaining in process (as of December 2, 2024)

Key eligibility criteria

- Age ≥18 to ≤35 years
- SCD with β^S/β^S, β^S/β^0, or β^S/β^+ genotypes
- ≥4 sVOCs in 24 months pre-screening
- No available matched sibling donor
- No history of overt stroke

Key safety endpoints

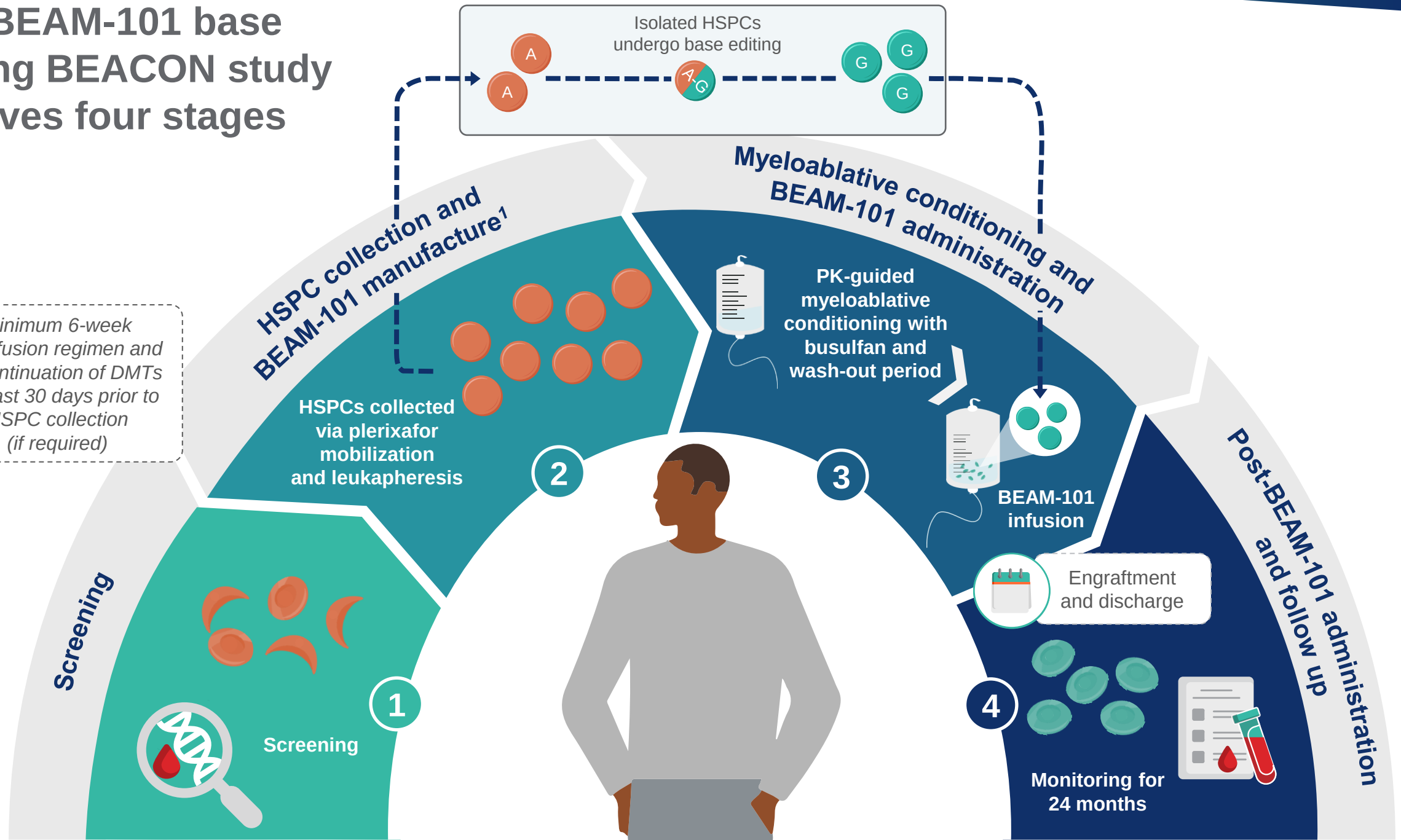
- Proportion of patients with successful neutrophil engraftment
- Time to neutrophil engraftment
- Time to platelet engraftment

Key efficacy endpoints

- Proportion of patients sVOC-free for 12 consecutive months
- Total Hb levels
- HbF and HbS levels
- Hemolysis parameters
- Patient-reported outcomes
- RBC function and organ damage

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)
DMC, Data Monitoring Committee; HbF, fetal hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell; SCD, sickle cell disease; SRC, Safety Review Committee; sVOC, severe vaso-occlusive crisis

The BEAM-101 base editing BEACON study involves four stages



1. Kopesky P, et al. Poster presented at EHA; Jun 2024; Madrid, Spain

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

Baseline demographics and characteristics of patients treated with BEAM-101

Baseline characteristics	N=7
Age (years), mean (range)	22.6 (19–27)
Sex, n (%)	
Male	4 (57.1)
Female	3 (42.9)
Genotype, n (%)	
β^S/β^S	6 (85.7)
β^S/β^0	1 (14.3)
Race, n (%)	
Black or African American	7 (100)
Previous hydroxyurea use, n (%)	7 (100)
Alpha globin loci genotype, n (%)	
0 deletions	4 (57.1)
1 deletion	3 (42.9)
Investigator-reported severe VOCs in the 2 years prior to start of study, mean (range)	10.3 (7–13)

Safety and efficacy analysis: N=7

Length of follow up in analysis set: 11 months (range: 1–11)

Data cutoff Oct 28, 2024

To qualify as a severe VOC, 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. ACS, acute chest syndrome; Hb, hemoglobin; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; VOC, vaso-occlusive crisis

BEAM-101 treatment characteristics

Dosing	N=7
Number of mobilization and apheresis cycles, mean (range)	1.4 (1–2)
Busulfan cumulative AUC (µg*h/mL), mean (range)	73.9 (61.8–83.2)
BEAM-101 dose infused ($\times 10^6$ CD34+ cells/kg) mean (range)	10.7 (3.2–23.4)
Duration (months) of follow up after BEAM-101 dosing, mean (range)	5.6 (1.4–11.0)
Day of last RBC transfusion, median (range)	15 (7–122*)

BEAM-101's efficient manufacturing process resulted in patients requiring few collection cycles

Data cutoff Oct 28, 2024

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

*One patient required blood transfusions up to Day 122 as part of ongoing management of critical illness; excluding this patient, the mean (range) last day of RBC transfusion is 11.8 (7–17)

AUC, area under the curve; RBC, red blood cell

BEAM-101 treatment and engraftment characteristics

Dosing	N=7
Number of mobilization and apheresis cycles, mean (range)	1.4 (1–2)
Busulfan cumulative AUC (µg*h/mL), mean (range)	73.9 (61.8–83.2)
BEAM-101 dose infused ($\times 10^6$ CD34+ cells/kg) mean (range)	10.7 (3.2–23.4)
Duration (months) of follow up after BEAM-101 dosing, mean (range)	5.6 (1.4–11.0)
Day of last RBC transfusion, median (range)	15 (7–122*)
Time to neutrophil engraftment (days), mean (range)	17.1 (15–21)
Duration of neutropenia (ANC <500 cells/µL), (days), mean (range)	6.3 (4–9)
Time to platelet engraftment (days), mean (range)	19.1 (11–34)

Patients had rapid neutrophil and platelet engraftment with a low number of neutropenic days

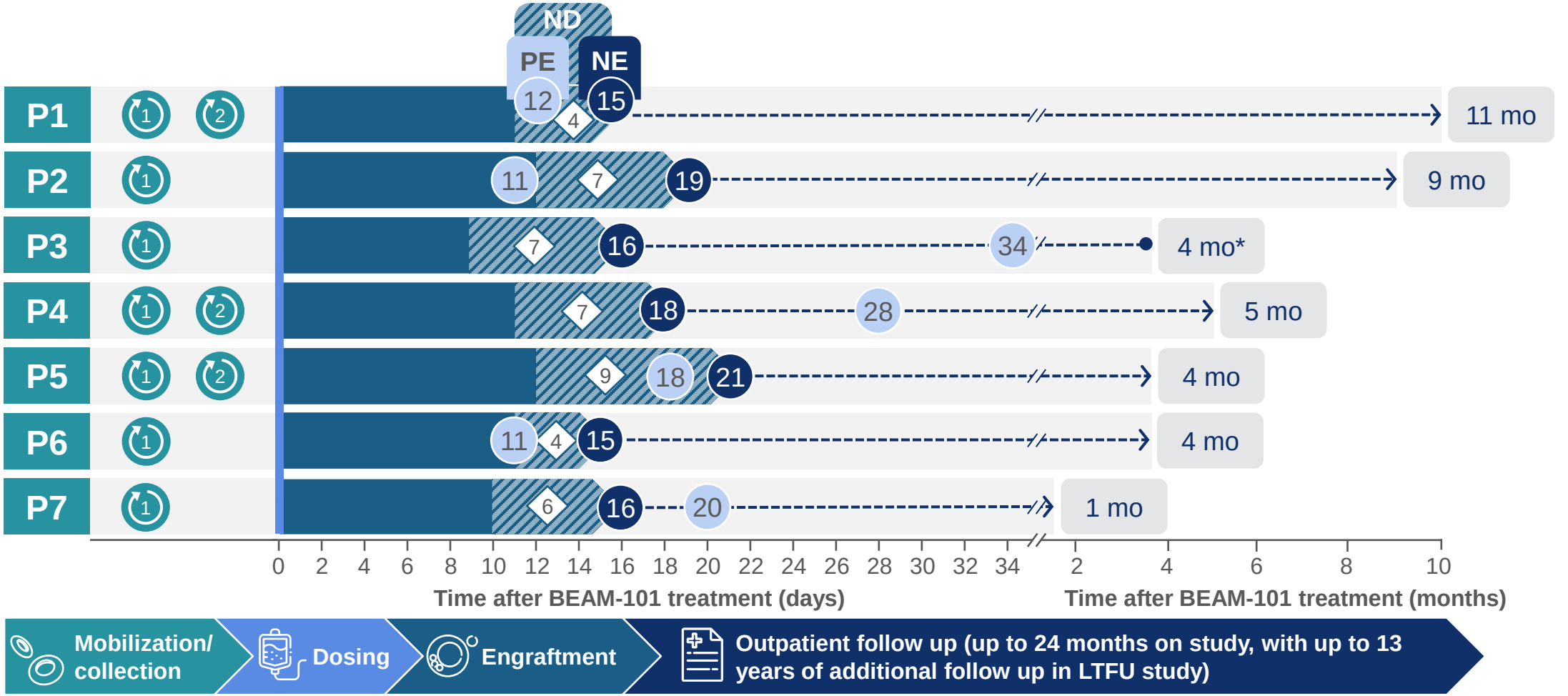
Data cutoff Oct 28, 2024

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 per µL on 3 separate days without receiving a platelet transfusion for at least 7 days prior to the first of the 3 measurements through to the last measurement

*One patient required blood transfusions up to Day 122 as part of ongoing management of critical illness; excluding this patient, the mean (range) last day of RBC transfusion is 11.8 (7–17)

ANC, absolute neutrophil count; AUC, area under the curve; RBC, red blood cell

BEAM-101 and its treatment process aim to minimize mobilization and engraftment burden



Data cutoff Oct 28, 2024. Patients remain as inpatients until neutrophil engraftment has occurred, and the patient is deemed clinically stable for discharge and outpatient management. Patients assessed at daily intervals to evaluate engraftment success status. Patients will be discharged home after neutrophil engraftment. Platelet engraftment may be monitored in the outpatient setting on a weekly basis. *P3 died due to refractory respiratory failure 4 months after infusion. LTFU, long-term follow up; mo, month; ND, neutropenic days; NE, neutrophil engraftment; P, patient; PE, platelet engraftment

Day of neutrophil engraftment
Day of platelet engraftment
Mobilization cycle
Daily monitoring
Neutropenic days
Follow up

BEAM-101 initial safety data are consistent with busulfan conditioning and autologous HSCT

Patients with, n (%)	N=7
Any TEAEs	7 (100)
Related to BEAM-101	1 (14.3)
Any TEAEs ≥Grade 3	7 (100)
Related to BEAM-101	0
AEs leading to discontinuation	0
Serious TEAEs	4 (57.0)
Related to BEAM-101	0
Death	1
Related to BEAM-101	0

- Most common TEAEs (≥3 patients) included febrile neutropenia*, stomatitis*, skin hyperpigmentation, pharyngeal inflammation, anemia*, edema peripheral, decreased appetite*, headache, hypervolemia, hypokalemia
- All but 1 non-serious TEAE (Grade 1 dizziness) were assessed as not related to BEAM-101
- No serious TEAEs occurred in >1 patient

No patients have experienced any VOCs post-engraftment

Data cutoff Oct 28, 2024

Related events include events where investigator has assessed relationship as possibly or definitely related to BEAM-101

*Includes events that were ≥Grade 3 in at least 3 patients

AE, adverse event; HSCT, hematopoietic stem-cell transplantation; TEAE, treatment-emergent adverse event

One patient died due to respiratory failure, likely related to busulfan conditioning, 4 months after infusion

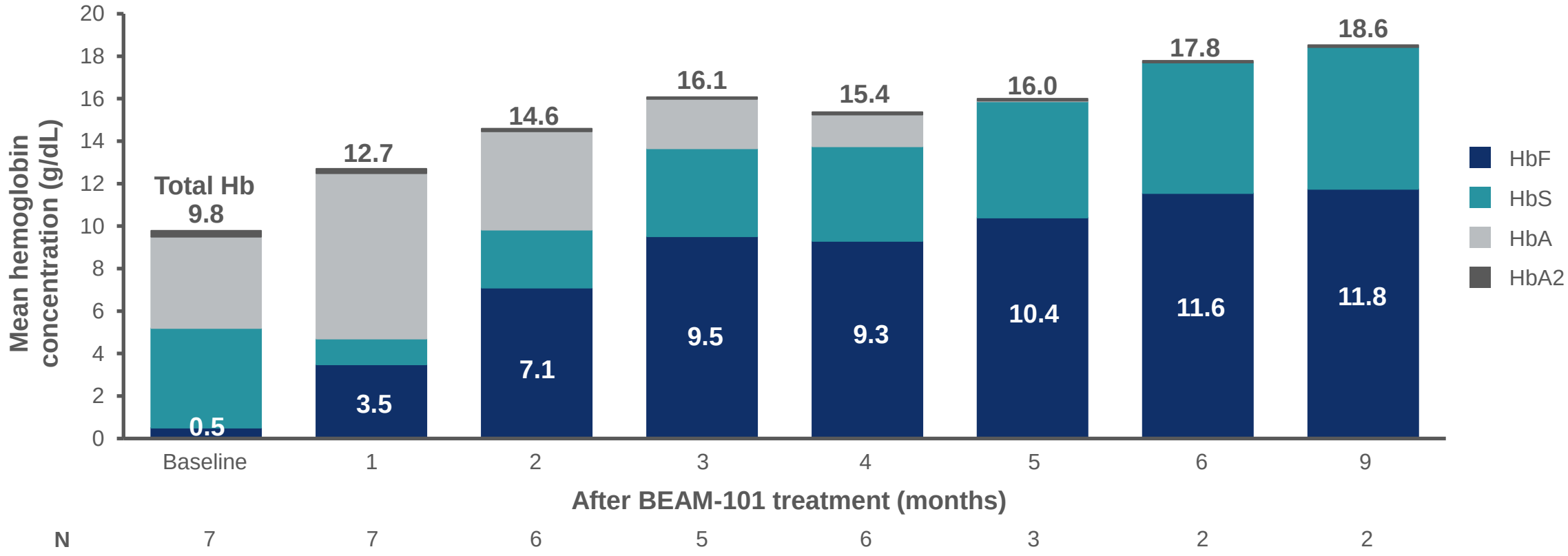
P3 medical history	• Female / 21 yrs / β^S/β^S with history of SCD with ACS, severe VOCs, obstructive sleep apnea, and e-cigarette use
Conditioning and dosing	• Conditioned with busulfan dose of 0.8 mg/kg Q6H x 4 days, cumulative AUC of 74.2 µg•h/mL • Busulfan dose and AUC within protocol target • Cell dose: 6.2 $\times 10^6$ CD34+ cells/kg • Neutrophil engraftment on Day 16, platelet engraftment on Day 34
Event course	• Admitted Day 58 with fever, vomiting, diarrhea; then developed respiratory distress with multiple pulmonary infiltrates • Infection or hemorrhage ruled out, patient discharged home on Day 82 with steroids and nocturnal BiPAP • Readmitted 4 days later with progressive respiratory distress, acute lung injury and pneumomediastinum consistent with idiopathic pneumonia syndrome (IPS)*, requiring mechanical ventilation • Patient died due to refractory respiratory failure, at 4 months after BEAM-101 infusion
Investigator assessment	• **Event was not related to BEAM-101** • Fatal event of respiratory failure likely related to busulfan conditioning, which has known pulmonary toxicity, resulting in IPS • Possible contributing factor was e-cigarette use (vaping)

The DMC concluded:
'The occurrence of severe pulmonary toxicity is in keeping with known risks with busulfan'

*Defined as diffuse alveolar injury with multi-lobar pneumonia, absence of infection or other etiology (cardiac, etc.), along with hypoxemia
ACS, acute chest syndrome; AUC, area under the curve; BiPAP, bilevel positive airway pressure; DMC, data monitoring committee; e-cigarette, electronic cigarette; ICU, intensive care unit; P, patient; Q6H, every 6 hours; SCD, sickle cell disease; VOC, vaso-occlusive crises

Patients achieved rapid and robust HbF induction with corresponding HbS reduction

All patients achieved endogenous HbF >60% and HbS <40% by 1 month after BEAM-101 treatment



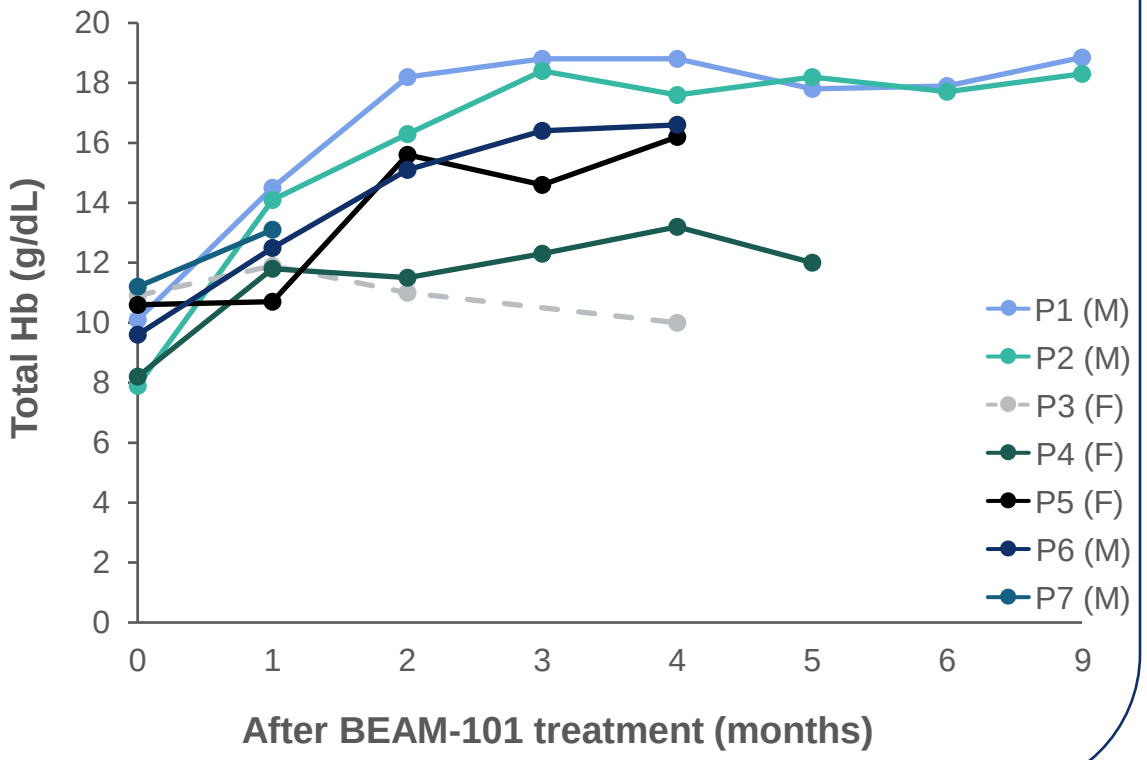
N	7	7	6	5	6	3	2	2
%HbF (HbF/HbF+HbS)	10%	74%	72%	70%	67%	65%	65%	64%

Data cutoff Oct 28, 2024

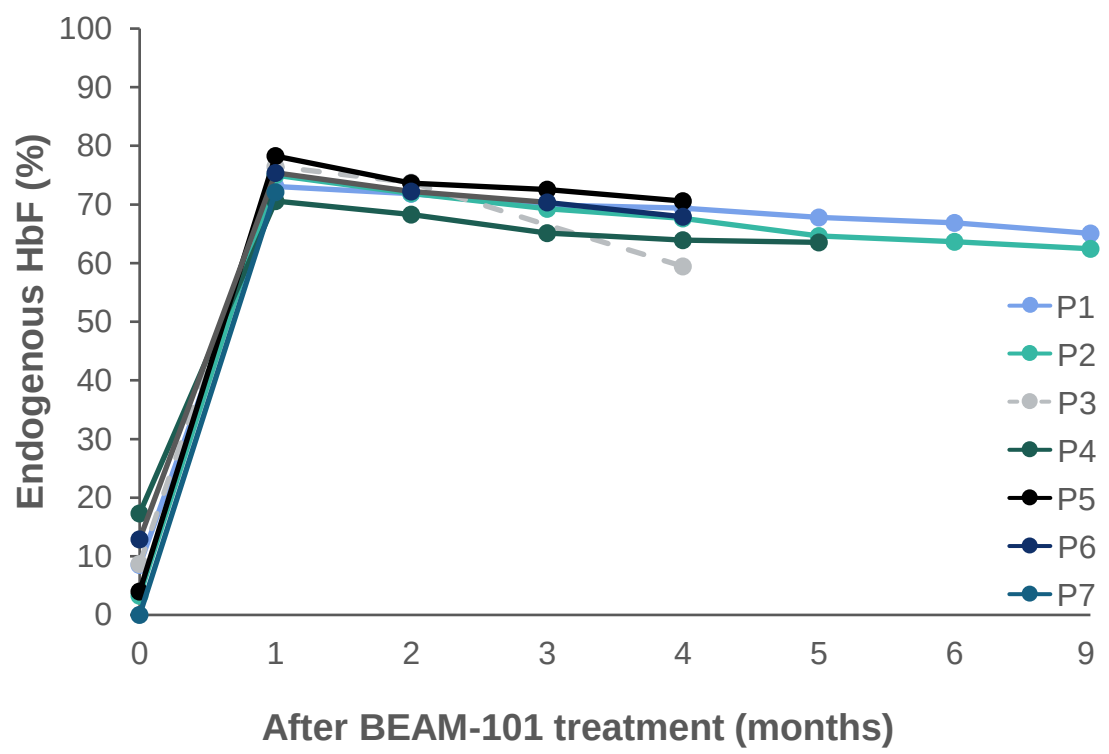
Female total Hb LLN-ULN: 11.5-15 g/dL; Male LLN-ULN: 13-17 g/dL. Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; LLN, lower limit of normal; ULN, upper limit of normal

All patients had rapid and robust increases in total Hb and HbF that were sustained through follow up

Robust increase in total Hb that is stable through follow up



Rapid and robust increase in % endogenous HbF that remained >60% through follow up



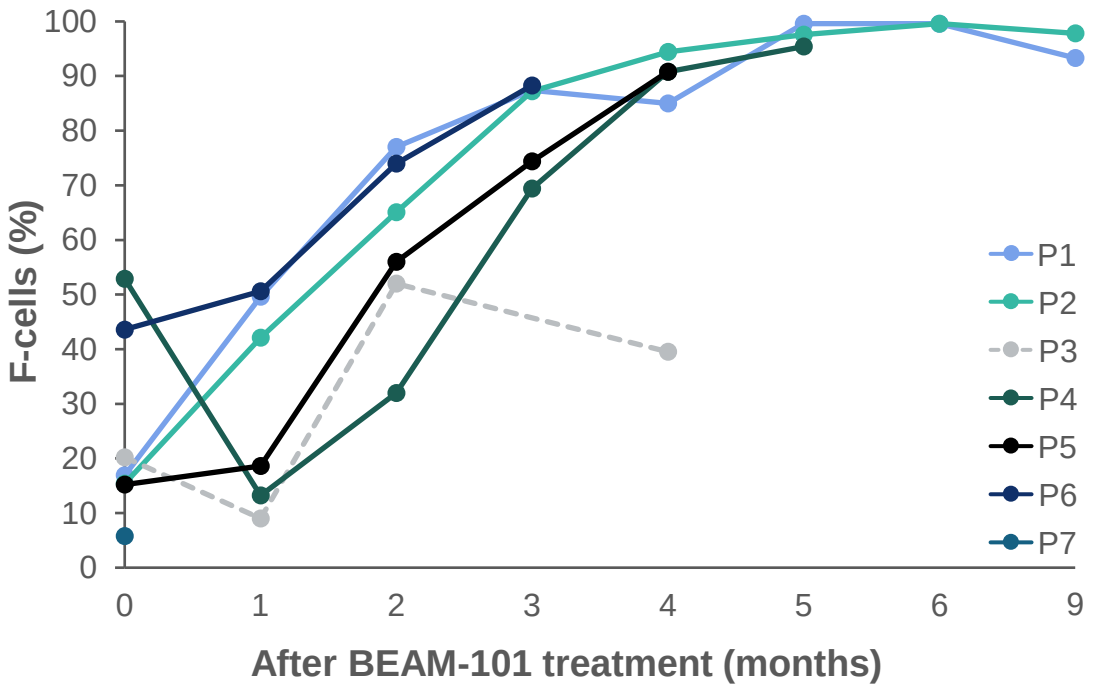
Data cutoff Oct 28, 2024

Female total Hb LLN-ULN: 11.5-15 g/dL; Male LLN-ULN: 13-17 g/dL

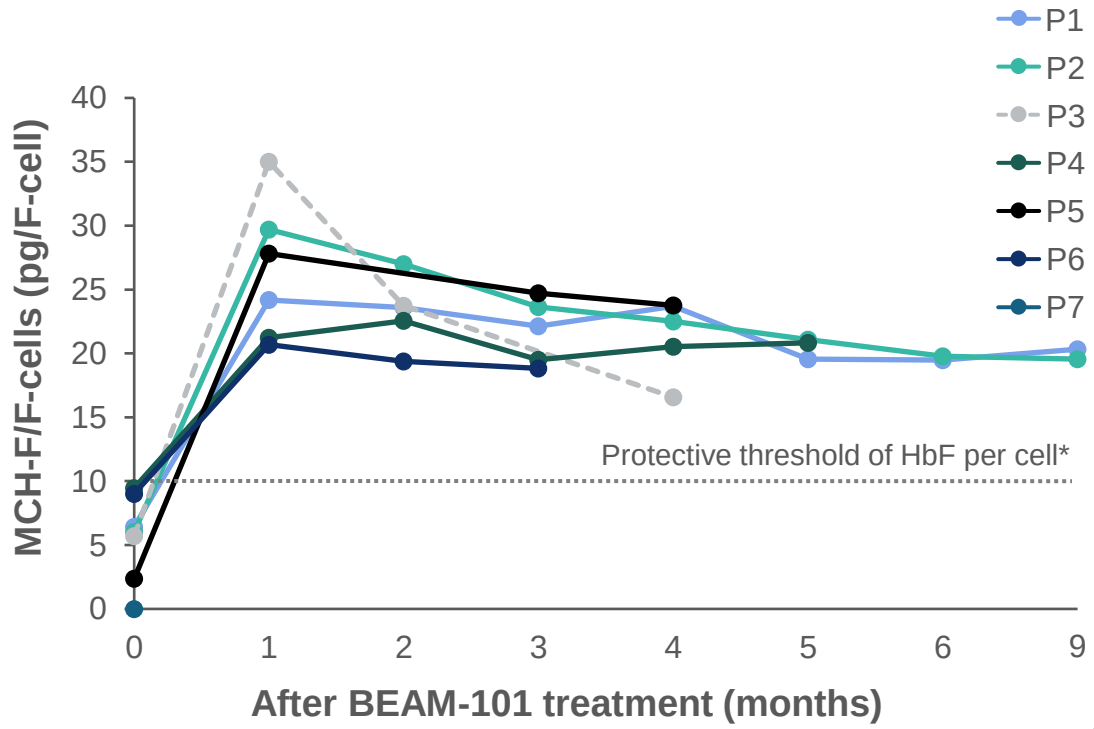
Hb, hemoglobin; HbF, fetal hemoglobin; F, female; M, male

Pancellular distribution of HbF observed through follow up

Pancellular HbF expression observed following elimination of transfused blood



Mean HbF (pg/cell) reached the protective threshold by M1 and were sustained through follow up



Visit Poster 4957 on Dec 9th for further details on HbF and HbS expression and biomarker analyses exploring RBC health and function from the BEACON study

Data cutoff Oct 28, 2024

*Defined as the level of HbF that inhibits deoxyHbS polymerization; Steinberg MH, et al. Blood 2014;123:481–485

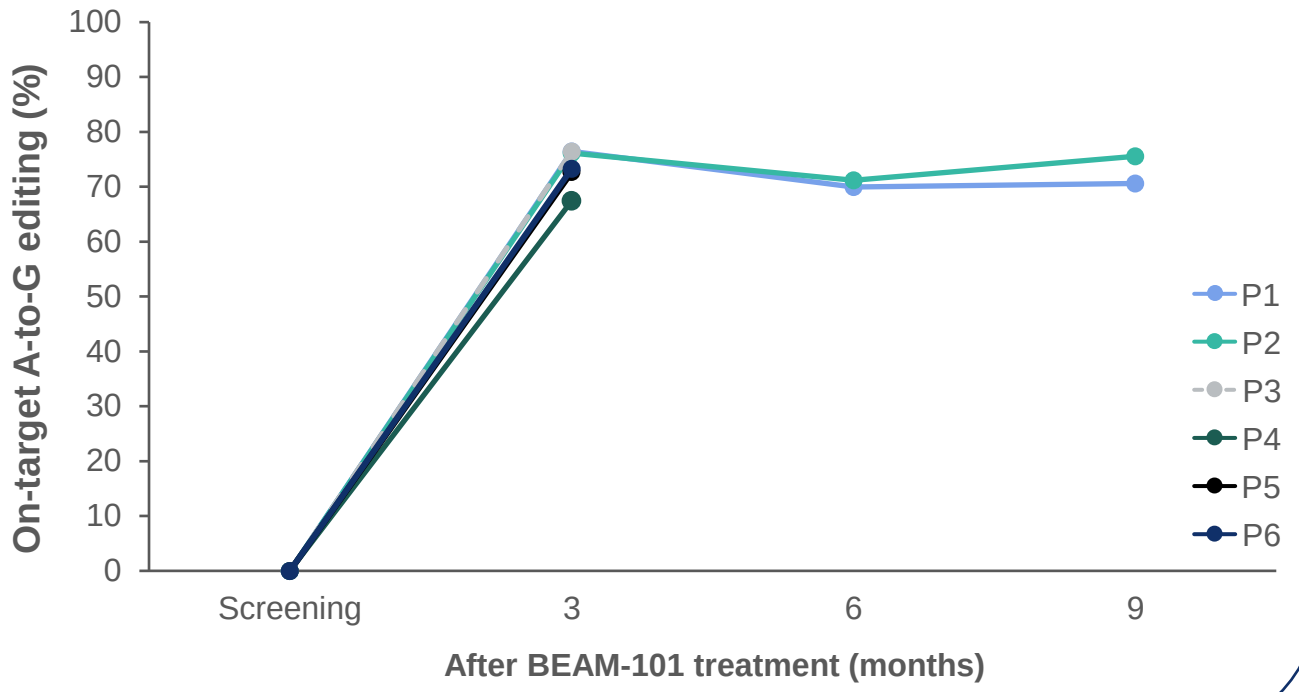
F-cell, HbF-containing cell; HbF, fetal hemoglobin; HbS, sickle hemoglobin; M, month; MCH, mean corpuscular hemoglobin; P, patient

High editing rates in peripheral blood following BEAM-101 treatment indicate successful engraftment and persistence of gene-edited cells

High % editing in BEAM-101 drug product

Patient	On-target A-to-G editing (%)
1	93
2	92
3	90
4	93
5	92
6	94

Early data show consistent high levels of persistent editing in peripheral blood after BEAM-101 treatment



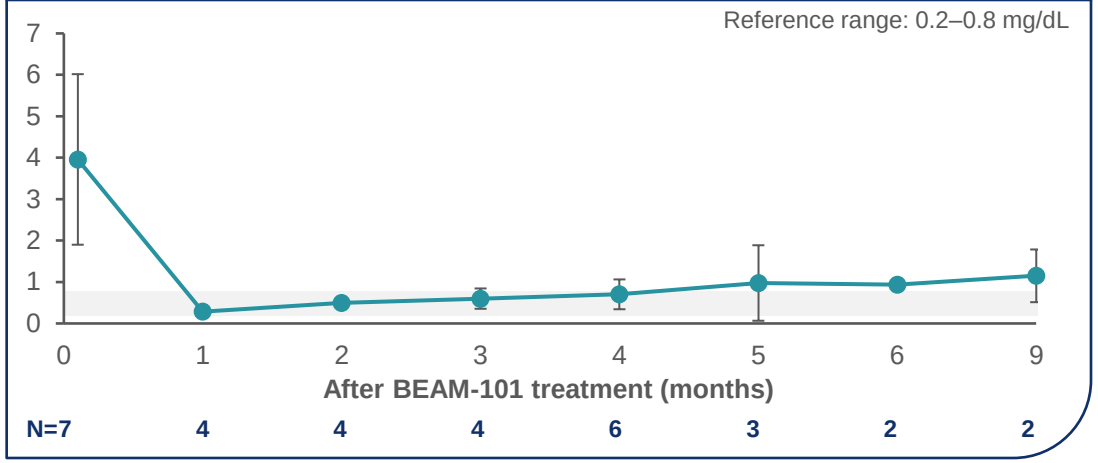
Data cutoff Oct 28, 2024

Percent of target bases that undergo A-to-G edit; Percent of editing from the drug product release is measured at day 14 of in vitro erythroid differentiation by NGS

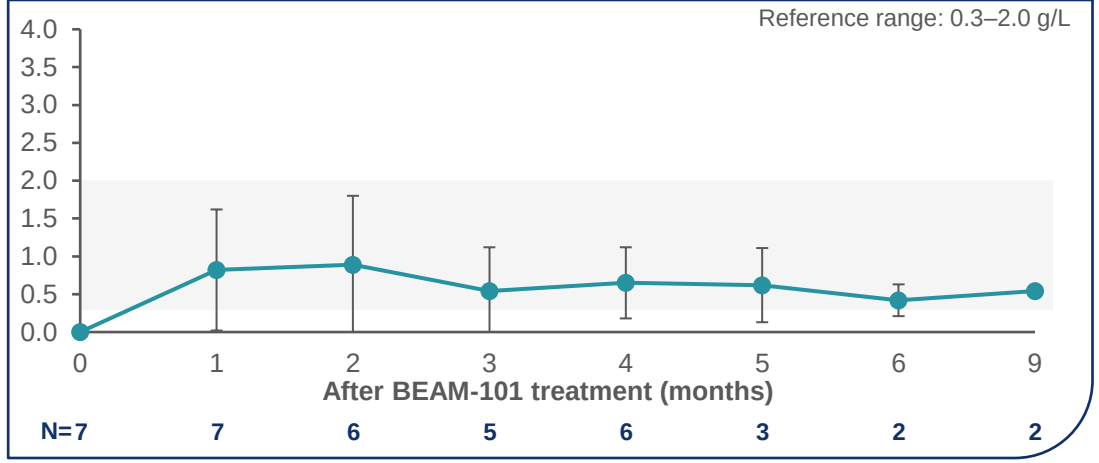
NGS, next-generation sequencing; P, patient

Hemolysis markers normalized or improved following BEAM-101 treatment

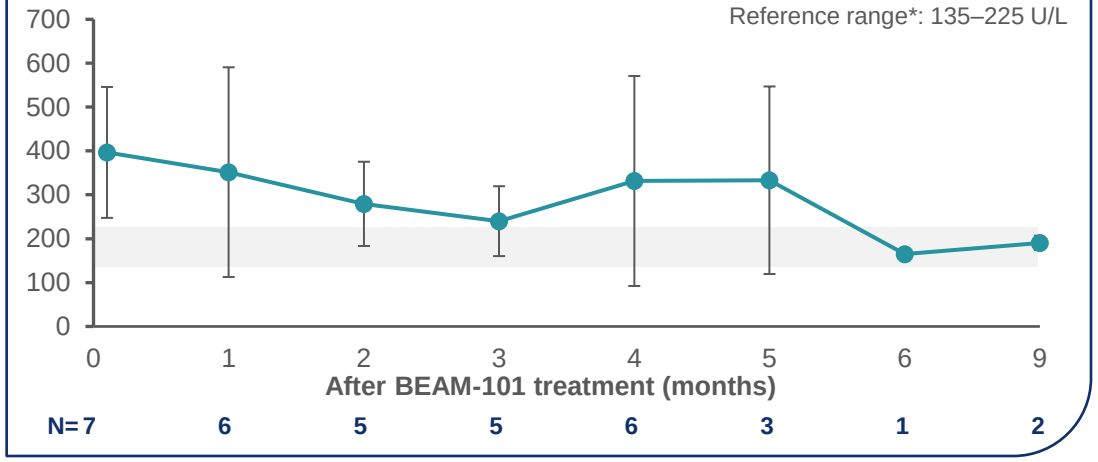
Indirect bilirubin (mg/dL ± SD)



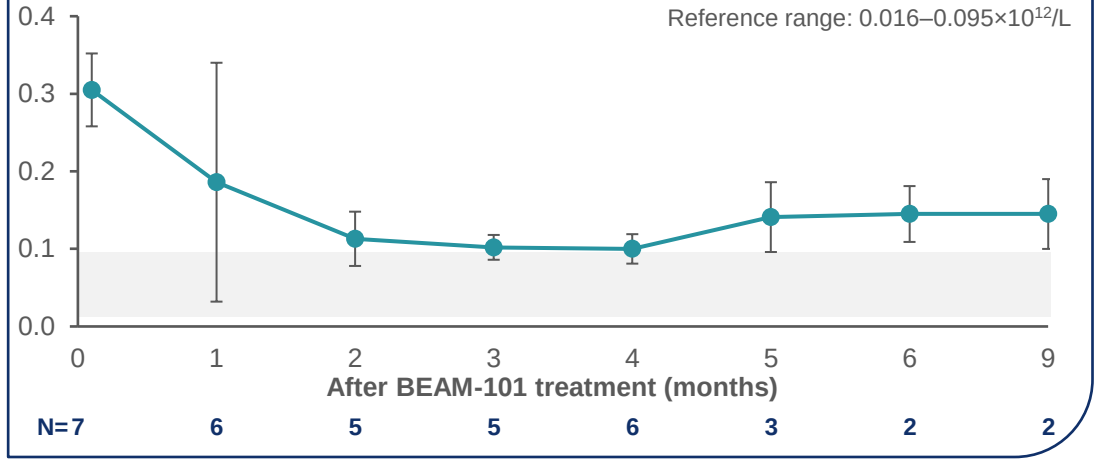
Haptoglobin (g/L ± SD)



Lactate dehydrogenase (U/L ± SD)



Reticulocytes (×10^{12}/L ± SD)



Data cutoff Oct 28, 2024

*Reference range shows lower limit of normal for male/female; higher limit of normal for male. SD, standard deviation

Conclusions

- Patients treated with BEAM-101 required a **low number of mobilization cycles**, and achieved **rapid neutrophil and platelet engraftment** with low number of neutropenic days
- **Initial safety data with BEAM-101 are consistent with busulfan conditioning and autologous HSCT**, with **no VOCs reported** by investigators post-engraftment
- All patients achieved **rapid and robust increases in total Hb and HbF**; **pancellular** distribution of HbF was **maintained above protective thresholds** through follow up
- All patients achieved **rapid and robust decrease in HbS**, and markers of hemolysis were **normalized or improved** in all patients

Initial data from the BEACON study support base editing and BEAM-101 as **safe,** and effective in leading to **robust and sustained increases in HbF expression** and **resolution of anemia** in SCD patients

HbF, fetal hemoglobin; HbS, sickle hemoglobin; HSCT, hematopoietic stem-cell transplantation; SCD, sickle cell disease; VOC, vaso-occlusive crisis

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