Red blood cell (RBC) health and function post BEAM-101 treatment: multiple exploratory biomarkers demonstrate rheology and sickling parameters comparable to sickle cell trait (SCT)

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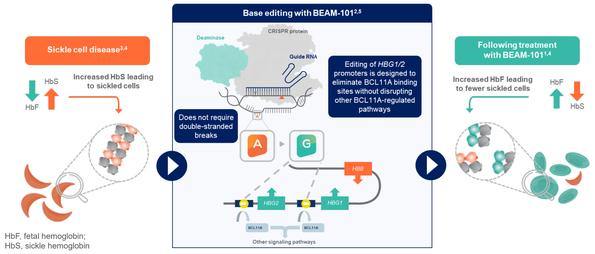
Introduction

- 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

BEACON is a Phase 1/2 study evaluating the safety and efficacy of BEAM-101 in patients with SCD and severe vaso-occlusive crises (VOCs)

Figure 2: BEACON study design

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 24 months 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* ► 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

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

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**
- 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 hematopoietic stem cell transplant (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

References

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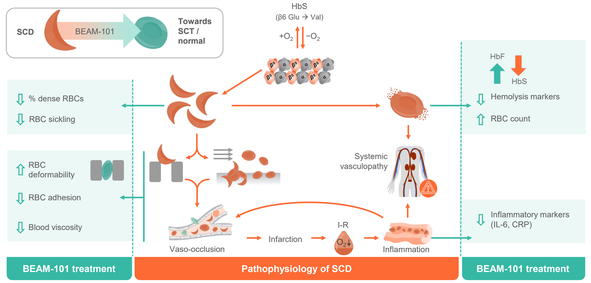
Aim

What would improved RBC health and function look like post BEAM-101 treatment?

Figure 3: Impact of BEAM-101 treatment on RBC health and function

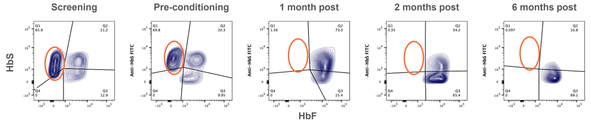


Data cutoff April 2025 for the biomarker data presented here. CRP, C-reactive protein; HbF, fetal hemoglobin; HbS, sickle hemoglobin; IL, interleukin; I-R, ischemia reperfusion; RBC, red blood cell; SCD, sickle cell disease; SCT, sickle cell trait

Results

99% of non-transfused RBCs expressed HbF as early as Month (M) 1 post BEAM-101

Figure 4: HbF and HbS expression in non-transfused RBCs following treatment with BEAM-101

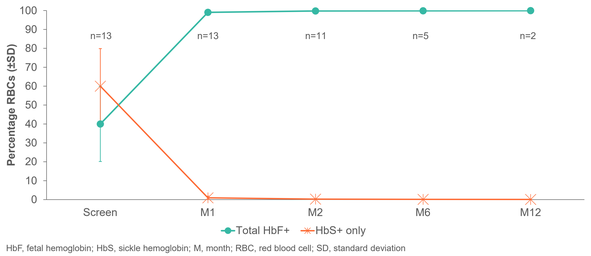


Example data shown for patient 1 analysis excluding transfused cells. HbS+ only cells are marked in orange circles. FITC, fluorescein isothiocyanate; HbF, fetal hemoglobin; HbS, sickle hemoglobin; Q, quadrant; RBC, red blood cell

Methods

- **HbF/HbS cellular expression:** Whole blood samples were processed, fixed, and double stained for measuring HbF and HbS relative expression using labeled antibodies followed by a duplex flow cytometry assay
- Cells were gated to measure HbF/HbS in four quadrants as % of
  - S-positive and F-negative (S^+ and F^-) RBC
  - S-positive and F-positive (S^+ and F^+) RBC
  - S-low and F-positive (S^{low} and F^+) RBC
  - S-negative and F-negative (S^- and F^-) RBC
- Percentage of cells in each quadrant was determined
- Transfused S- and F-cells were gated out in the analysis

Figure 5: Increasing HbF with near elimination of HbS expression post BEAM-101



HbF, fetal hemoglobin; HbS, sickle hemoglobin; M, month; RBC, red blood cell; SD, standard deviation

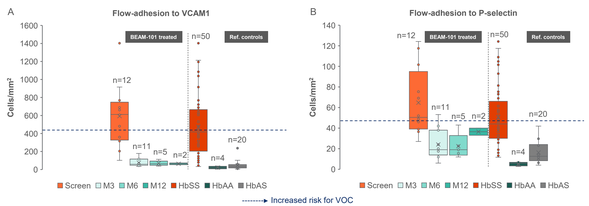
Samples: Patients 1–13

- Mean total HbF+ cells as a percentage of non-transfused cells increased to >99% as early as M1, remained >99% at M2, M6, and M12
- Mean RBC expressing solely HbS decreased to <1% at M1, <0.3% at M2, <0.2% at M6, and <0.1% at M12

Reduced cellular adhesion post BEAM-101, to levels comparable to SCT

- Adhesion indices for vascular cell adhesion molecule 1 (VCAM1)/P-selectin were well below the critical SCD indices for VOC risk (dashed blue lines, **Figure 6**)[6,7] and were comparable to SCT reference samples post BEAM-101

Figure 6: Flow-adhesion of whole blood to VCAM1 and P-selectin



A) Flow adhesion to VCAM1; B) Flow adhesion to P-selectin. HbAA, healthy volunteer; HbAS, sickle cell trait; HbSS, sickle cell disease; VCAM1, vascular cell adhesion molecule 1. o, individual data points; x, mean; -, median

Methods

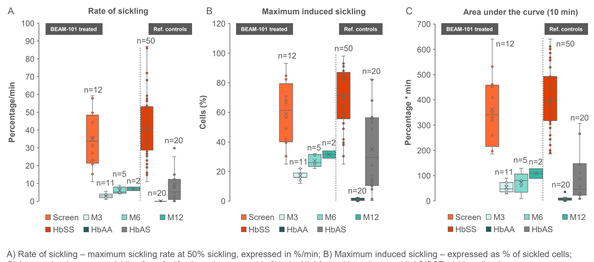
- Whole blood samples were perfused through VCAM1 (**Figure 6A**) or P-selectin (**Figure 6B**) -coated microfluidic channels using pulsatile shear stress and washed with buffer at the same flow rate to eliminate non-adhering cells. Images were acquired and analyzed with an imaging software[7]

Samples: BEAM-101 Study patients 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13; HbAS SCT and HbAA reference controls

Reduced sickling post BEAM-101, to levels at or below SCT

- Rate of sickling (**Figure 7A**) and maximum induced sickling (**Figure 7B**) decreased to levels comparable to SCT reference samples post BEAM-101
- Area under the curve in the sickling assay decreased to levels comparable to SCT post BEAM-101 (**Figure 7C**)

Figure 7: Improvement in sickling kinetics post-BEAM 101



A) Rate of sickling – maximum sickling rate at 50% sickling, expressed in %/min; B) Maximum induced sickling – expressed as % of sickled cells; C) Area under the curve – sickling from 0–10 min and expressed in %*min. HbAA, healthy volunteer; HbAS/SCT, sickle cell trait; HbSS, sickle cell disease; M, month. o, individual data points; x, mean; -, median

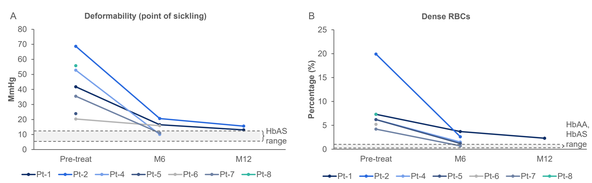
Methods

- Real-time sickling kinetics were captured using the dynamic sickling assay (DSA)[8]

Samples: BEAM-101 study patients 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13; HbAS SCT and HbAA reference controls

Improved deformability and reduced percentage of dense red blood cells (%DRBC) post BEAM-101, achieving SCT levels

Figure 8: Changes in deformability (PoS) and %DRBCs following treatment with BEAM-101



A) Point of Sickling from LORRCA indicating deformability; B) % dense red blood cells (%DRBCs). LORRCA, Laser Assisted Optical Rotational Cell Analyzer; M, month

Methods

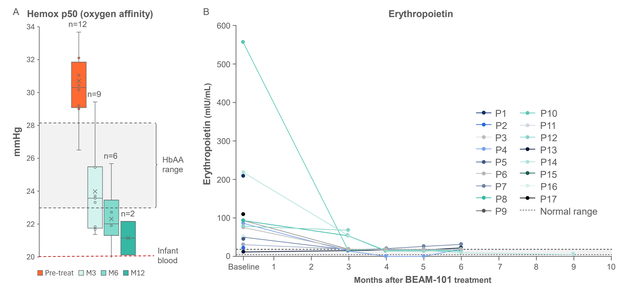
- Point of Sickling (PoS) is a measure of deformability. Reduced PoS indicates increased/improved deformability
- %DRBC is measured using ADVIA

Samples: BEAM-101 study patients 1, 2, 4, 5, 6, 7, 8

Oxygen affinity increased and erythropoietin decreased post BEAM-101

- The partial pressure at which HbF is half saturated with oxygen (p50) is 19 mmHg, compared with 27 mmHg for HbA[9]. HbF has a higher affinity for oxygen, binds oxygen more readily. Oxygen affinity increased post BEAM-101 (**Figure 9A**)
- Decreased erythropoietin following treatment indicates improvements in systemic oxygen delivery (**Figure 9B**)

Figure 9: Oxygen affinity and erythropoietin following treatment with BEAM-101

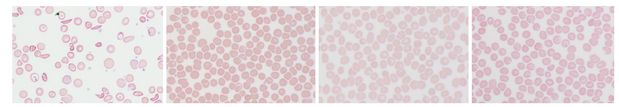


A) Hemox p50, reduced p50 indicates higher oxygen affinity; B) Erythropoietin. HbAA, healthy volunteer; M, month; P, patient. o, individual data points; x, mean; -, median

RBC morphology improved post BEAM-101

- Abnormal morphology and sickle cells at pre-treatment resolved post BEAM-101

Figure 10: Changes in RBC morphology following treatment with BEAM-101



B

Observation	Definition	Grade pre-treatment	Grade post-treatment
Sickle cells	Sickled RBC	1+ to 3+	Not detected
Polychromasia	Immature RBC	1+ to 2+	Not detected
Hypochromia	RBC of less color	1+ to 2+	Not detected
Elongated or crescent-shaped cells	Cells of abnormal shape and size	1+ to 2+	Not detected

3+ = ~≥10%
2+ = ~5–9%
1+ = ~1–4%

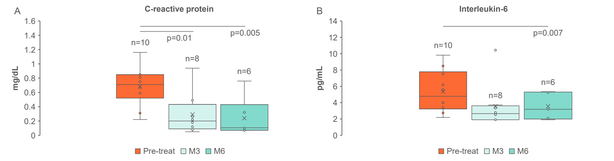
A) RBC morphology pre- and post-treatment. Images are representative from patient 2; B) Improvements in RBC morphology post-treatment. M, month; P, patient; RBC, red blood cell

Samples: BEAM-101 study patients 1–13

Reduced systemic inflammation post BEAM-101

- Reductions in C-reactive protein (CRP) and interleukin-6 (IL-6) were seen post BEAM 101, indicating a decrease in systemic inflammation

Figure 11: Changes in inflammatory markers following treatment with BEAM-101



A) serum CRP; B) serum IL-6 measured using ELISA assays. ELISA, enzyme-linked immunosorbent assay; M, month. o, individual data points; x, mean; -, median

Samples: BEAM-101 study patients 1–10

Conclusions

Based on data from exploratory biomarkers in up to 13 patients, treatment with BEAM-101 led to:

- **99%** of non-transfused RBCs **expressing HbF**, **with near-complete elimination** of RBCs expressing **solely HbS**, as early as **M1 post BEAM-101**
- Decrease in **cell adhesion to VCAM and P-selectin** to significantly **below the critical SCD threshold**, indicating a **reduced risk for VOCs**
- **Flow adhesion of whole blood** indices **comparable to SCT** (HbAS), indicating a potential **improvement in RBC** and **vascular health**
- Decrease in **multiple sickling parameters** to levels at or **below SCT**
- Improvement in **RBC deformability**
- Decreased **%DRBCs** and resolution of **abnormal RBC morphology**
- Reduced **systemic inflammation**

Emerging data across multiple RBC assays suggest that BEAM-101 treatment restored RBC health and function, indicating a reversal of SCD pathophysiology, and support base editing with BEAM-101 as a potentially transformative therapeutic modality for the treatment of patients with SCD

Beam THERAPEUTICS