Impact of BEAM-101 Treatment on Red Blood Cell Hemoglobin Expression, Rheology and Sickling Properties: Initial Data from the BEACON Phase 1/2 Study of Autologous CD34+ Base Edited Hematopoietic Stem Cells in Sickle Cell Disease

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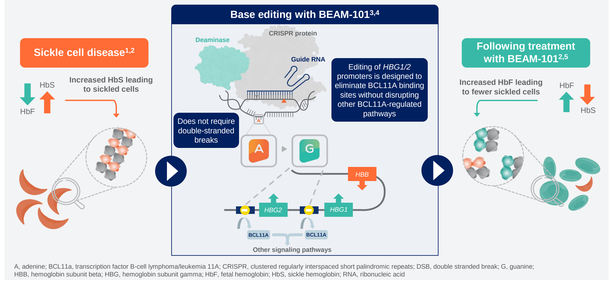
Introduction

BEAM-101 uses precise base editing to increase levels of fetal hemoglobin (HbF)

- BEAM-101 is an investigational cell therapy comprising autologous CD34+ hematopoietic stem cells that are base edited to introduce A-to-G substitutions into the *HBG1/2* gene promoters to disrupt BCL11A binding, leading to increased HbF production

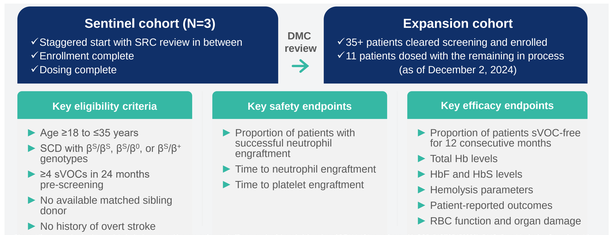
Figure 1: BEAM-101 mechanism of action



A, adenine; BCL11a, transcription factor B-cell lymphoma/leukemia 11A; CRISPR, clustered regularly interspaced short palindromic repeats; DSB, double stranded break; 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 the safety and efficacy of BEAM-101 in patients with sickle cell disease (SCD) and severe vaso-occlusive crises (VOCs)

Figure 2: Study design



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

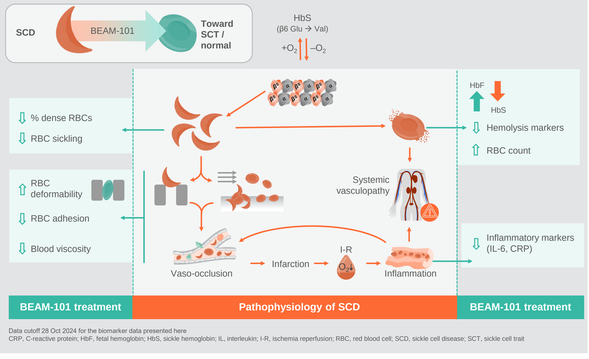
Initial data from the BEACON study support base editing and BEAM-101 as safe, and effective in leading to robust and sustained increases in HbF expression and resolving anemia in SCD patients[6]

01	Patients treated with BEAM-101 required a **low number of mobilization and collection cycles**, and achieved **rapid neutrophil and platelet engraftment** with low number of neutropenic days
02	**Initial safety data with BEAM-101 are consistent with busulfan conditioning and autologous HSCT**, with **no VOCs reported** by investigators post-engraftment
03	All patients achieved **rapid and robust increases in total Hb and HbF; pancellular** distribution of HbF was **maintained above protective thresholds** through follow up. HbF was >60% by 1 month after BEAM-101 dosing
04	All patients achieved **rapid and robust decrease in HbS**, and markers of hemolysis were **normalized or improved** in all patients. HbS was <40% by 1 month after BEAM-101 dosing

Aim

What would improved red blood cell (RBC) health and function look like post BEAM-101 treatment?

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

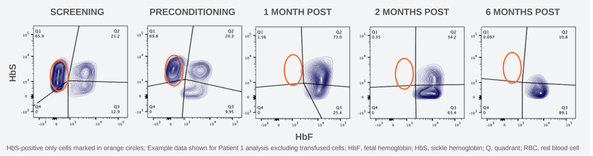


Data cutoff 28 Oct 2024 for the biomarker data presented here
CRP, C-reactive protein; HbF, fetal hemoglobin; HbS, sickle hemoglobin; IL, interleukin; I-R, ischemia reperfusion; RBC, red blood cell; SCD, sickle cell disease; SCT, sickle cell trait

Results

High HbF and low HbS-positive RBCs post BEAM-101

Figure 4: HbF and HbS cellular expression following treatment with BEAM-101



HbS-positive only cells marked in orange circles; Example data shown for Patient 1 analysis excluding transfused cells; HbF, fetal hemoglobin; HbS, sickle hemoglobin; Q, quadrant; RBC, red blood cell

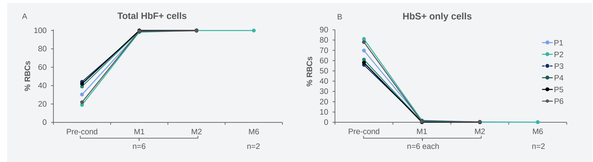
Methods

- HbF/HbS cellular expression was measured using whole blood samples, which 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^-) RBCs (Q1)
  - S-positive and F-positive (S^+ and F^+) RBCs (Q2)
  - S-low and F-positive (S^{low} and F^+) RBCs (Q3)
  - S-negative and F-negative (S^- and F^-) RBCs (Q4)
- The percentage of cells in each quadrant was determined
- Transfused S^- F^- cells were gated out in the analysis

Samples: Screening, preconditioning, Month (M)1, M2, samples were available for the first six patients; M6 samples were available for Patient (P)1 and 2 only

High HbF and low HbS-positive RBCs post BEAM-101

Figure 5: Changes in HbF and HbS following treatment with BEAM-101



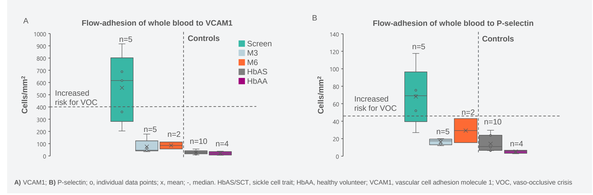
A) Total HbF+ RBCs; **B)** HbS+ only RBCs; Cond, conditioning; HbF, fetal hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell

- More than 98% of non-transfused RBCs express HbF (total HbF+ cells) at M1 which increased to >99% at M2 and later
- RBC expressing solely HbS decreased to <2% at M1, <0.4% at M2 and <0.1% at M6

Reduced cellular adhesion post BEAM-101

- Adhesion indices for vascular cell adhesion molecule 1 (VCAM1)/P-selectin were well below the critical SCD indices for VOC risk (dashed blue lines)[7,8] post BEAM-101
- Adhesion indices VCAM1/P-selectin were comparable to HbAS reference samples post BEAM-101

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



A) VCAM1; **B)** P-selectin; o, individual data points; x, mean; -, median. HbAS/SCT, sickle cell trait; HbAA, healthy volunteer; VCAM1, vascular cell adhesion molecule 1; VOC, vaso-occlusive crisis

Methods

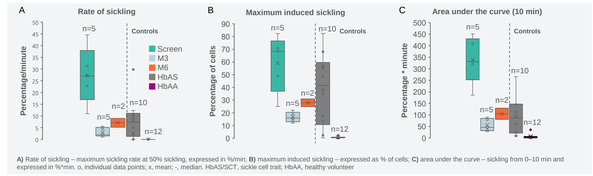
- Whole blood samples were perfused through **(A)** VCAM1- or **(B)** P-selectin-coated microfluidic channels using pulsatile shear stress and washed with buffer at the same flow rate to eliminate non-adhering cells. Images were acquired and analyzed with an imaging software[8]

Samples: Screening and M3 for P1, P2, P4, P5, P6. M6 for P1, P2. HbAS SCT samples and HbAA samples were tested for reference ranges

Reduced sickling post BEAM-101

- Sickling parameters decreased post BEAM-101 to levels comparable to samples from HbAS individuals

Figure 7: Sickling is reduced following treatment with BEAM-101



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

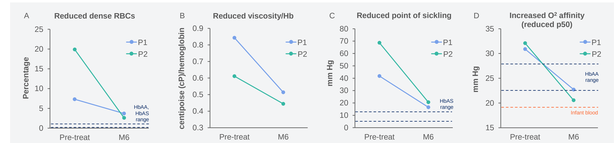
Methods

- Real-time sickling kinetics were captured using the dynamic sickling assay (DSA)[9]

Samples: Screening and M3 for P1, P2, P4, P5, P6. M6 for P1, P2. HbAS SCT samples and HbAA samples were tested for reference ranges

Improved hemorheology post BEAM-101

Figure 8: Impact of BEAM-101 on hemorheology



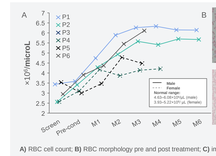
Whole blood was used to measure **A)** density using ADVIA, **B)** viscosity with cone and plate viscometer, shear rate of 45; **C)** deformability using oxygen gradient ektacytometry to determine point of sickling (PoS); and **D)** p50 for oxygen affinity through hemox[10]

Samples: Screening, preconditioning, M6 for P1 and P2. Screening or preconditioning data points were used as pretreatment data based on sample/data availability

Improved RBC count and morphology post BEAM-101

- Abnormal morphology and sickle cells at pretreatment resolved post BEAM-101 along with an increase in RBC count

Figure 9: Impact of treatment with BEAM-101 on RBC count and morphology



C	Observation	Definition	Grade pretreatment	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
	Abnormal cells	Cells of abnormal shape & size	1+ to 2+	Not detected

3+ = ≥10%, 2+ = ~5–9% , 1+ = ~1–4%

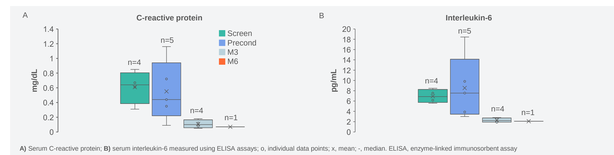
A) RBC cell count; **B)** RBC morphology pre and post treatment; **C)** improvements in RBC morphology post treatment. RBC, red blood cell

Samples: Screening, preconditioning, M1, M2, M3, M4, M5, M6 for P1, P2, P4, P5, P6; for P4, P5, P6 only samples collected until date included

Reduced inflammatory signals post BEAM-101

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

Figure 10: Impact of BEAM-101 on inflammation



A) Serum C-reactive protein; **B)** serum interleukin-6 measured using ELISA assays; o, individual data points; x, mean; -, median. ELISA, enzyme-linked immunosorbent assay

Samples: Screening, preconditioning, and M3 for P1, P2, P4, P5, P6; M6 for P2

Conclusions

Based on available data on exploratory biomarkers in up to six patients:

- More than 98% of non-transfused RBCs express HbF at M1, which increased to >99% at M2 and M6 with near complete elimination of RBCs expressing solely HbS post BEAM-101
- Cell adhesion reduced to significantly below the critical SCD threshold post BEAM-101, indicating a reduced risk for VOCs. Adhesion indices post BEAM-101 were comparable to HbAS reference samples indicating a potential improvement in RBC and vascular health
- Changes in multiple sickling parameters and reduction in RBC sickling were comparable to HbAS post BEAM-101 treatment
- Percentage of dense RBCs, blood viscosity, oxygen affinity, and RBC deformability improved post BEAM-101 treatment
- Increase in RBC cell number and resolution of abnormal RBC morphology observed post BEAM-101
- Emerging data across multiple assays suggest that BEAM-101 treatment restored RBC health and function, indicating a reversal of SCD pathophysiology, and support BEAM-101 as a potentially transformative therapeutic modality for the treatment of patients with SCD

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