Ristoglogene autogetemcel treatment restored red blood cell health and function in patients with sickle cell disease, with sickling and rheology parameters comparable to sickle cell trait

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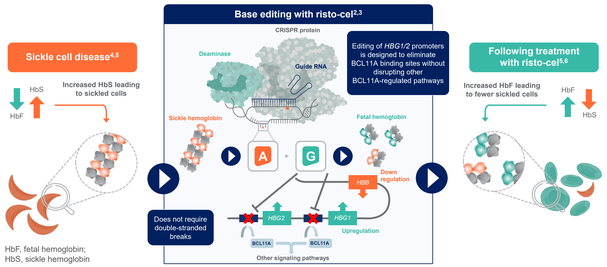
Introduction

- Ristoglogene autogetemcel (risto-cel, BEAM-101), an investigational cell therapy, consists of autologous CD34+ hematopoietic and progenitor stem cells base edited at the *HBG1/2* gene promotors to disrupt BCL11A repressor binding, enabling re-expression of γ-globin and production of anti-sickling fetal hemoglobin (HbF) (**Figure 1**)[1]
- Biomarkers for red blood cell (RBC) health and function were measured pre and post treatment to ascertain the impact of risto-cel on sickle cell disease (SCD) pathophysiology (**Figure 2 and 3**)[2]

Figure 1: Risto-cel uses precise base editing to increase levels of HbF[2,3]



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

Figure 2: BEACON study design

Key eligibility criteria	Key safety endpoints	Key efficacy endpoints
▶ Age ≥12 to ≤35 years	▶ Proportion of patients with successful neutrophil engraftment	▶ Proportion of patients sVOC-free for 12 consecutive months*
▶ SCD with βS/βS, βS/β0, or βS/β+ genotypes	▶ Proportion of patients with successful platelet engraftment	▶ Total Hb levels
▶ ≥4 sVOCs in 2 years prior to screening	▶ Time to neutrophil engraftment	▶ HbF and HbS levels
▶ No available matched sibling donor	▶ Time to platelet engraftment	▶ Hemolysis parameters
▶ No history of overt stroke		▶ RBC function and organ damage
		▶ Editing efficiency in blood and bone marrow

Phase 1/2, non-randomized, open-label, single-arm, multicenter, safety and efficacy study of the administration of risto-cel 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) and 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 VOC; VOC, 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[1]

- Risto-cel'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 risto-cel are consistent** with busulfan conditioning, autologous hematopoietic stem cell transplant, and underlying SCD
- **No sVOCs were reported** by investigators post engraftment
- All patients achieved **rapid and robust increases in total hemoglobin (Hb) and HbF (>60%)**; **pancellular** distribution of HbF was **maintained above the protective threshold of 10 pg HbF/F-cell** through follow up[6]
- All patients achieved **rapid and robust decrease in sickle hemoglobin (HbS) (<40%) with resolution of anemia**, and markers of hemolysis were **normalized or improved** in all patients
- Post risto-cel, at M6 (n=29), **the mean endogenous HbF was 63.5%** and **HbS was 36.2%**

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Disclosure

All Beam Therapeutics authors hold Beam Therapeutics stocks and/or options

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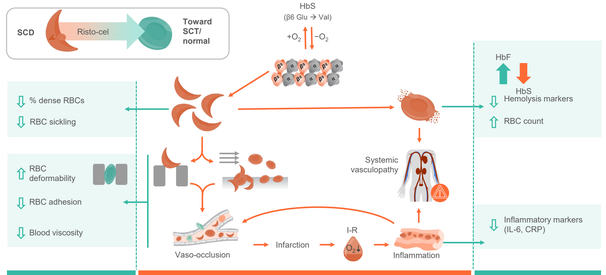
Aim

We present exploratory RBC biomarker data from BEACON (NCT05456880), an ongoing, Phase 1/2, single-arm, open-label, multicenter study evaluating the safety and efficacy of risto-cel in patients with SCD and recurrent sVOCs (**Figure 2**)

Figure 3: What would improved RBC health and function look like post risto-cel treatment?

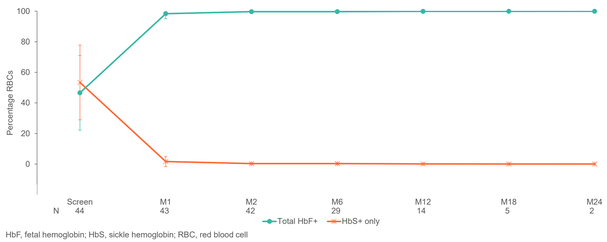


Data cutoff February 27, 2026 for the biomarker data presented here. CRP, C-reactive protein; HbF, fetal hemoglobin; HbS, sickle hemoglobin; IL, interleukin; I-R, ischemia reperfusion; RBC, red blood cell; SCD, sickle cell disease; SCT, sickle cell trait

Results

Over 98% of non-transfused RBCs expressed HbF as early as Month (M) 1 post risto-cel

Figure 4: Increasing total HbF+ cells with near elimination of HbS+ only cells post risto-cel



HbF, fetal hemoglobin; HbS, sickle hemoglobin; RBC, red blood cell

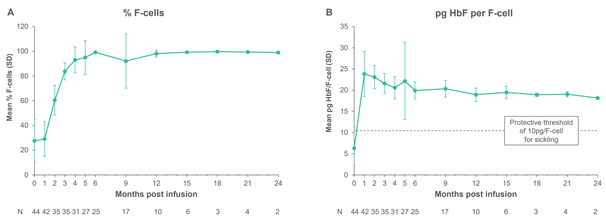
- Mean RBC expressing solely HbS decreased to <1.7% at M1, <0.4% at M2, <0.4% at M6, <0.2% at M12, <0.1% at M18 and M24
- Mean total HbF+ cells as a percentage of non-transfused cells increased to >98% as early as M1, reached >99% at M2 and remained >99% at M6, M12, 18 and 24

Methods

- **Cellular HbF vs HbS expression in RBCs (Figure 4):** Whole blood samples were collected from patients at screen, M1, 2, 3, 6, 12, 18, and 24. They were then fixed, permeabilized, and double stained for HbF and HbS, followed by duplex flow cytometry to measure HbF and/or HbS-expressing RBCs

Pancellular HbF expression sustained at protective levels post risto-cel

Figure 5: HbF expression continues to demonstrate pancellularity and protective thresholds post risto-cel



Dashed line in (B) represents the protective threshold (HbF ≥10 pg). HbF, fetal hemoglobin; SD, standard deviation

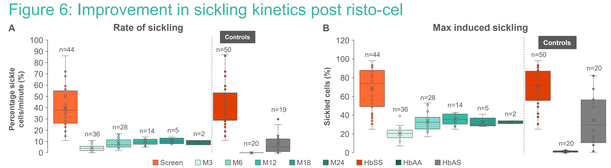
- In total peripheral blood at M6, mean % F-cells was 99.24% (range, 97.0–99.9) with a mean of 19.92 pg HbF/F cell, well above the protective threshold against sickling[6]

Methods

- **Percentage of HbF-expressing RBCs (F-cells) (Figure 5):** Whole blood samples were collected from patients at screen, M1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24. HbF-expressing RBC percentage was determined in a singleplex flow cytometry assay

Sickling parameters reduced post risto-cel to levels at or below sickle cell trait (SCT)

Figure 6: Improvement in sickling kinetics post risto-cel



o, individual data points; x, mean; –, median. HbSS, HbAA, and HbAS samples were tested for reference ranges
HbAA, healthy volunteer; HbAS, sickle cell trait; HbSS, sickle cell disease; M, month

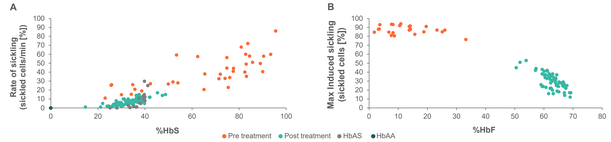
- Rate of sickling (**Figure 6A**) and max induced sickling (**Figure 6B**) were reduced post risto-cel and remained at levels comparable to SCT through follow up

Methods

- **Sickling assay (Figure 6):** Samples for sickling were collected at screen, M3, 6, 12, 18, and 24. Sickling kinetics were captured in real-time using the dynamic sickling assay (DSA)™ in microfluidic channels where cells sickle under enzymatically induced hypoxic conditions[7]

Induction of HbF resulted in reduced sickling post risto-cel

Figure 7: Association of %HbF and %HbS with sickling

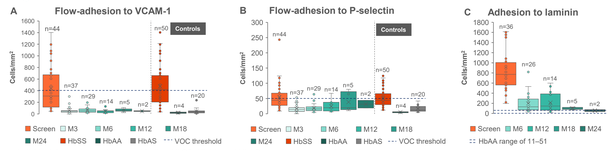


In Figure 7B, pre treatment samples with >10%HbA were removed in the %HbF analysis to eliminate effects of transfused blood on %HbF levels HbAA, healthy volunteer; HbAS, sickle cell trait; HbF, fetal hemoglobin; HbS, sickle hemoglobin

- Higher %HbS in the blood correlate with increased rate of sickling pre treatment, and both parameters reduced post treatment to levels comparable to SCT (HbAS) (**Figure 7A**)
- Higher HbF levels correlate with reduced sickling post risto-cel (**Figure 7B**)

Cellular adhesion reduced post risto-cel to levels comparable to SCT

Figure 8: Flow-adhesion of whole blood to VCAM-1, P-selectin, or laminin



o, individual data points; x, Mean; –, Median. HbSS, HbAA, and HbAS samples were tested for reference ranges
HbAA, healthy volunteer; HbAS, sickle cell trait; HbSS, sickle cell disease; M, month; VOC, vaso-occlusive crises; VCAM-1, vascular cell adhesion molecule 1

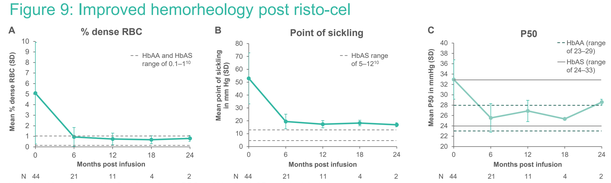
- Flow-adhesion indices for vascular cell adhesion molecule 1 (VCAM-1) (**Figure 8A**) and P-selectin (**Figure 8B**) were well below the critical SCD indices for VOC risk (dashed blue line, **Figure 8A** and **8B**) and were comparable to SCT reference samples post risto-cel up to M24[8,9]
- Post risto-cel indices for laminin reduced to levels comparable to HbAA (**Figure 8C, dashed line**)

Methods

- **Adhesion assay (Figure 8):** Whole blood samples were perfused through VCAM-1-, P-selectin- or laminin-coated microfluidic channels using pulsatile shear stress and real-time images were captured. VCAM-1 and P-selectin whole blood samples were collected at screen, M3, 6, 12, 18, and 24 and laminin samples were collected at screen, M6, 12, 18, and 24

Improved % dense RBCs (%DRBC), deformability, and O_2 affinity post risto-cel, achieving SCT levels

Figure 9: Improved hemorheology post risto-cel



HbAA, healthy volunteer; HbAS, sickle cell trait; RBC, red blood cell; SD, standard deviation

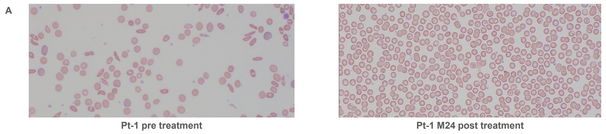
- %DRBC decreased, point of sickling (POS) was reduced (reflecting improved deformability), and O_2 affinity increased, collectively indicating improved hemorheology post risto-cel
- Viscosity under normoxia and hypoxia post risto-cel was lower than in HbSS samples (data not shown)

Methods

- **Hemorheology (Figure 9):** The %DRBC was quantified using an ADVIA system, while RBC deformability and the POS were assessed using a LORRCA ektacytometer. Samples were collected at screen, M6, 12, 18, and 24 (**Figure 9**)

RBC count and morphology improved post risto-cel

Figure 10: Changes in RBC count and morphology following treatment with risto-cel



B

Observation	Screen Grade	M3 Grade	M6 Grade	M12 Grade	M18 Grade	M24 Grade
Sickle cells	ND to 3+	ND	ND	ND	ND	ND
Polychromasia	ND to 3+	ND to 1+	ND to 1+	ND to 1+	ND to 1+	ND to 1+
Hypochromia	ND to 3+	ND to 1+	ND	ND	ND	ND
n	43	38	31	15	5	2

A) RBC morphology and B) Cell morphology grading: 1+ = ~1–4%; 2+ = ~5–9%; 3+ = ~>10%
M, month; ND, not detected; Pt, patient; RBC, red blood cell

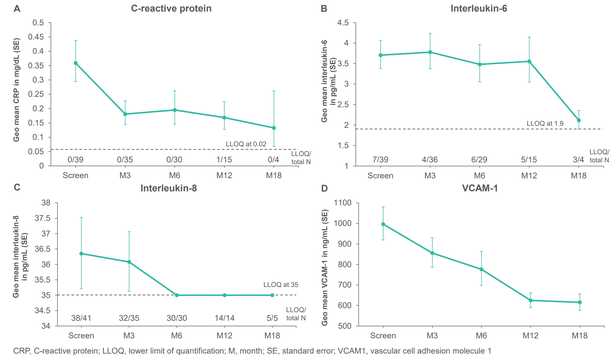
- Abnormal morphology and sickle cells at pre treatment assessment resolved post risto-cel with an increase in RBC count (**Figure 10**)
- Decreased erythropoietin following treatment indicates improvements in systemic oxygen delivery (data not shown)[1]
- Mean corpuscular volume remained normocytic, while mean corpuscular hemoglobin and hemoglobin concentration stayed within normal limits, with no increase through follow-up (data not shown)

Methods

- **RBC count and morphology (Figure 10):** RBC samples were collected at screen and at M1–24. They were counted directly from the whole blood using automated hematology analyzers. Morphology was determined primarily by microscopic examination of a stained peripheral blood smear, with increasing support from automated and digital morphology systems

Reduced systemic inflammation and adhesion post risto-cel

Figure 11: Reduced inflammatory and adhesion signals post risto-cel



CRP, C-reactive protein; LLOQ, lower limit of quantification; M, month; SE, standard error; VCAM1, vascular cell adhesion molecule 1

- Reductions in C-reactive protein (CRP) (**Figure 11A**), interleukin (IL)-6 (**Figure 11B**), IL-8 (**Figure 11C**), and VCAM-1 (**Figure 11D**) were seen post risto-cel, indicating a decrease in systemic inflammation and adhesion

Methods

- **Inflammatory and adhesion biomarkers (Figure 11):** CRP, IL-6, IL-8, and VCAM-1 were measured in serum using ELISA assays at screen, M3, M6, M12, M18, and M24

Conclusions

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

Based on updated biomarker data from the BEACON study in up to 44 patients, treatment with risto-cel led to:

- **Over 98%** of non-transfused RBCs **expressing HbF**, **with near-complete elimination** of RBCs expressing **solely HbS**, as early as **M1 post risto-cel**
- Sustained pancellular HbF expression above **protective levels**
- Restored RBC health, function, and hemorheology comparable to SCT levels, with **significantly decreased sickling and whole blood adhesion**
- **Reductions in sickling parameters** that showed lower variability than in SCT and approached HbAA levels, **suggesting robust correction of SCD pathophysiology**
- **Concurrent improvements in %DRBC, hemoglobin-O_2 affinity, and RBC deformability** comparable to established SCT thresholds
- **Improved RBC count and resolution of cellular morphology**
- **Reduction** in systemic inflammation and adhesion