(PS2332) 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

Topic: 26. Gene therapy, cellular immunotherapy and vaccination - Clinical

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Background

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). Red blood cell (RBC) health and function biomarkers were measured pre- and post- treatment to ascertain the impact of risto-cel on sickle cell disease (SCD) pathophysiology. Biomarkers included cellular HbF, HbS; whole-blood (WB) cell adhesion to vascular cell adhesion molecule 1 (VCAM-1); P-selectin or laminin; real-time sickling kinetics; hemorheology; and RBC morphology.

Aims

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 (pts) with SCD and frequent severe vaso-occlusive crises (VOC's).

Methods

WB samples were collected and stained for HbF (%F-cells) at screen, and post-risto-cel at months (M)1–6, 9, 12, 15, 18, 21, and 24, and HbF^+ vs HbS^+ cells at screen, M1, 2, 6, 12, 18, and 24 using singleplex and duplex flow cytometry, respectively. Adhesion and sickling assessment samples were collected at screen, M3, 6, 12, 18, and 24. For adhesion assays, samples were perfused through microfluidic channels coated with VCAM-1, P-selectin or laminin under shear stress and adhered cells were measured. Real-time sickling kinetics were analyzed using a dynamic sickling assay^{TM} to compare pre- and post-treatment study samples along with sickle (HbSS), normal (HbAA) and sickle cell trait (SCT; HbAS) blood reference samples. Oxygen affinity, deformability, RBC density, and cellular morphology were assessed.

Results

As of Jan 6, 2026, biomarker data for 43 pts with follow up ranging from M1–24 were available. Post-risto-cel, at M6 (n=26), the mean (standard deviation [SD]) endogenous HbF (HbF/[HbF+HbS]) was 63.7% (5.29) and HbS was 36.3% (5.29). In peripheral blood at M6 (n=15), mean (SD) %F-cells was 99.3% (0.71) with a mean (SD) of 20.57 (1.78) pg HbF per F-cell (n=14), above the 10 pg/cell anti-sickling threshold; these parameters stabilized thereafter. Duplex assay for HbF vs HbS expression showed >98% of HbF^+ cells, with near elimination of cells that were only HbS^+, as early as M1, which sustained during follow up to M24. Rate of sickling (Figure 1A) and max induced sickling (Figure 1B) were reduced post-risto-cel and remained at levels comparable to SCT through follow up. Post-risto-cel, adhesion indices for VCAM-1, P-selectin, and laminin were comparable to SCT. RBC density, oxygen affinity, and RBC deformability improved post-risto-cel. RBC morphology normalized post-treatment.

Summary/Conclusion

Updated RBC biomarker data from the BEACON study demonstrated that risto-cel treatment restored RBC health, function, and hemorheological parameters comparable to SCT levels, with significantly decreased sickling and RBC adhesion. Sickling parameter reductions were less variable than in SCT and even approached HbAA levels, indicating strong correction of SCD pathophysiology. Concurrent improvements were also found in RBC density, oxygen affinity, RBC deformability, and morphology, comparable to established SCT thresholds. Long-term follow-up biomarker data in additional pts continue to support base editing with risto-cel as a potentially transformative therapy for pts with SCD. Further data will be included in the final presentation.