Abstract: S273

Title: EXAGAMGLOGENE AUTOTEMCEL FOR SEVERE SICKLE CELL DISEASE

Abstract Type: Oral Presentation

Session Title: Stem cell transplantation - Clinical and cell therapy

Background:

Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy that reactivates fetal hemoglobin via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at erythroid-specific enhancer region of BCL11A. Exa-cel is approved as a one-time treatment for patients (pts) with severe sickle cell disease (SCD).

Aims:

Evaluate longer-term efficacy and safety of exa-cel in pts with SCD.

Methods:

CLIMB SCD-121 is a 24-month (mo), phase 3 trial of exa-cel in pts age 12-35y with SCD and a history of ≥2 VOCs/y in 2y prior to screening. Enrollment and dosing are complete; trial is ongoing. Primary efficacy endpoint is proportion of pts free of severe VOCs for ≥12 consecutive mos (VF12); key secondary efficacy endpoint is proportion of pts free from inpatient hospitalization for severe VOCs for ≥12 consecutive mos (HF12). Pts evaluable for VF12 and HF12 had ≥16 mos follow-up after exa-cel infusion. Evaluation of primary and key secondary endpoint began 60 days after last RBC transfusion for post-transplant support or SCD management. Pts completing trial enrolled in long-term follow-up Study 131. Mean (SD) shown except where noted.

Results:

As of 18 September 2023, 46 pts with SCD (age 21.4 [range 12-34]y; 12 [26.1%] age ≥12 to <18y; 4.2 VOCs/y at baseline) received exa-cel; median follow-up 22.3 (range 2.1-51.3) mos. 17 pts completed 2 yrs of follow-up in CLIMB SCD-121 and enrolled in Study 131. All pts engrafted neutrophils and platelets (median 27 and 34.5 days, respectively). 29/31 (93.5%) pts evaluable for primary endpoint were free of VOCs for ≥12 consecutive mos (VF12; 95% CI, 79%-99%; P<0.0001) and 31/31 (100%) were free from hospitalizations for VOCs for ≥12 consecutive mos (HF12; 95% CI, 89%-100%; P<0.0001). In pts achieving VF12, VOC free duration was 25.4 (range 18.0-48.7) mos. 27/29 pts remained VOC free; 1 pt had an adjudicated VOC after parvovirus infection ~22.8 mos after exa-cel (pt recovered and has been VOC-free [15.5 mos]) and 1 pt had a VOC after 30.5 mos of being VOC-free (pt has since been VOC-free for 1.0 mo) (Fig). Both pts maintained stable HbF and allelic editing levels. For all pts, mean total Hb was 11.9 g/dL at Month 3 and ≥11.0 g/dL from Month 6 onward; mean HbF was 37.1% at Month 3 and generally ≥ 40.0% from Month 6 onward with pancellular distribution (≥95% RBCs express HbF). Proportion of edited BCL11A alleles was stable in bone marrow CD34+ and peripheral blood nucleated cells. 39/46 pts (including those not yet evaluable) remained VOC free (up to 48.7 mos). Quality-of-life (QOL) measures showed significant improvements from baseline.

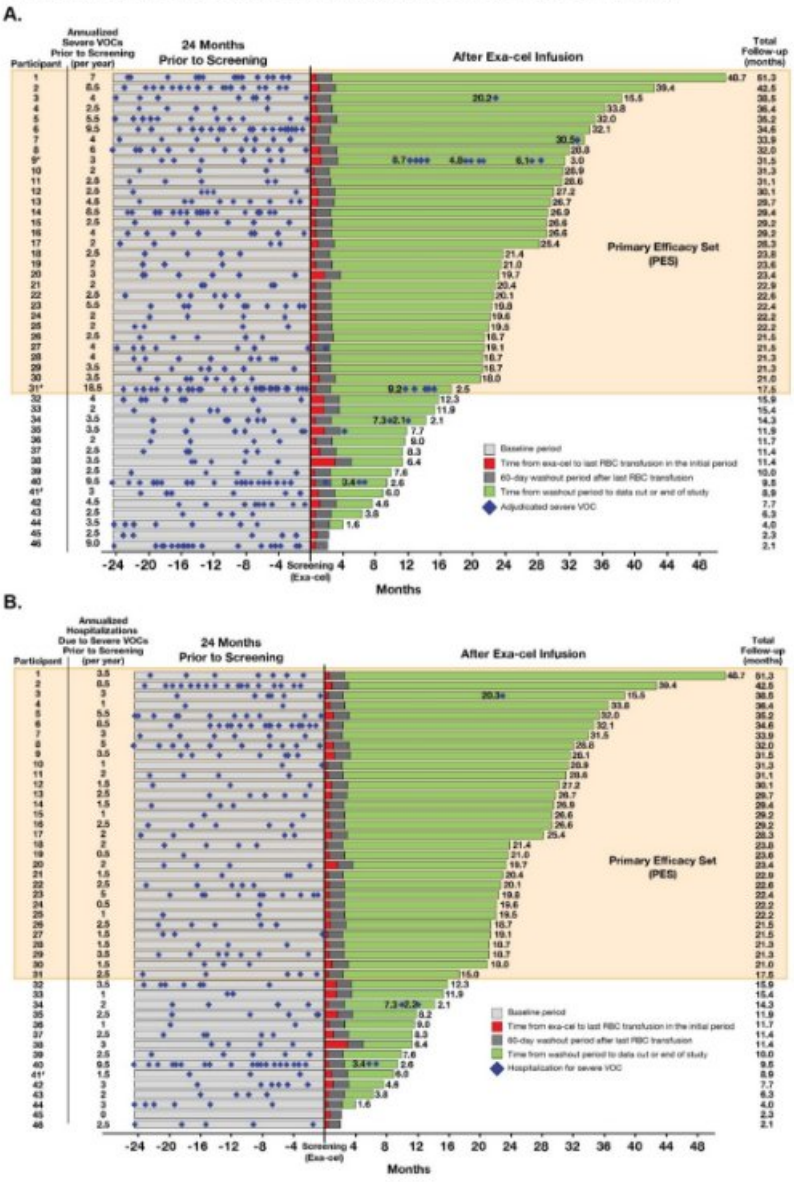
All pts had ≥1 adverse event (AE), most were Grade 1 or 2; 46 (100%) pts had AEs of Grade 3 or 4 severity. Most common AEs were nausea (67.4%), stomatitis (63.0%), vomiting (56.5%), febrile neutropenia (54.3%), headache (52.2%), and pruritis (50.0%). Most AEs and serious AEs (SAEs) occurred within first 6 mos. No pts had SAEs considered related to exa-cel. One pt died from respiratory failure due to COVID-19 pneumonia unrelated to exa-cel. There were no study discontinuations or malignancies.

Summary/Conclusion:

Exa-cel treatment led to early and sustained Hb and HbF increases, eliminating VOCs in ~94% of pts, eliminating inpatient hospitalization for VOCs in 100% of pts, and improving QOL, which was maintained over

the longer term. Safety profile remains generally consistent with myeloablative busulfan conditioning and autologous transplantation. These results confirm the potential for exa-cel to provide a one-time functional cure to pts with severe SCD.

Figure. Duration of Period Free From Vaso-Occlusive Crises (A) and Hospitalizations for Vaso-Occlusive Crises (B) (Study CLIMB SCD-121 and Study 131) After Exa-cel Infusion. All VOCs were adjudicated by the Independent Endpoint Adjudication Committee. Participants evaluable for the primary endpoint (VF12) and first key secondary endpoint (HF12) shows in tan box (primary efficacy set). *Participants who did not achieve VF12; #Death from respiratory failure due to COVID-19 infection.



Keywords: Sickle cell disease, Gene therapy