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ORAL ABSTRACTS

801.GENE THERAPIES

Exagamglogene Autotemcel for Severe Sickle Cell Disease

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Background: Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy designed to reactivate fetal hemoglobin via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of the BCL11A gene in patients (pts) with severe sickle cell disease (SCD). We report that in a pre-specified interim analysis, the pivotal CLIMB SCD-121 trial of exa-cel met primary and key secondary endpoints.
Methods: CLIMB SCD-121 is an ongoing, 24-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. Primary efficacy endpoint is proportion of pts free of severe VOCs for ≥12 consecutive months (mos) (VF12); key secondary efficacy endpoints are proportion of pts free from inpatient hospitalization for severe VOCs for ≥12 consecutive mos (HF12) and proportion of pts free from severe VOCs for ≥9 consecutive mos (VF9). Evaluable pts for VF12 and HF12 had ≥16 mos follow-up after exa-cel infusion; pts evaluable for VF9 had ≥12 mos follow-up after infusion. Evaluation of primary and key secondary endpoints 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) are shown except where noted.
Results: As of 10 Feb 2023, 42 pts with SCD (age 21.2[range 12-34]y; 12[28.6%] age ≥12 to <18y; 4.2 VOCs/y at baseline) received exa-cel. Following infusion, all pts engrafted neutrophils and platelets (median 27 and 34.5 days, respectively). 19/20

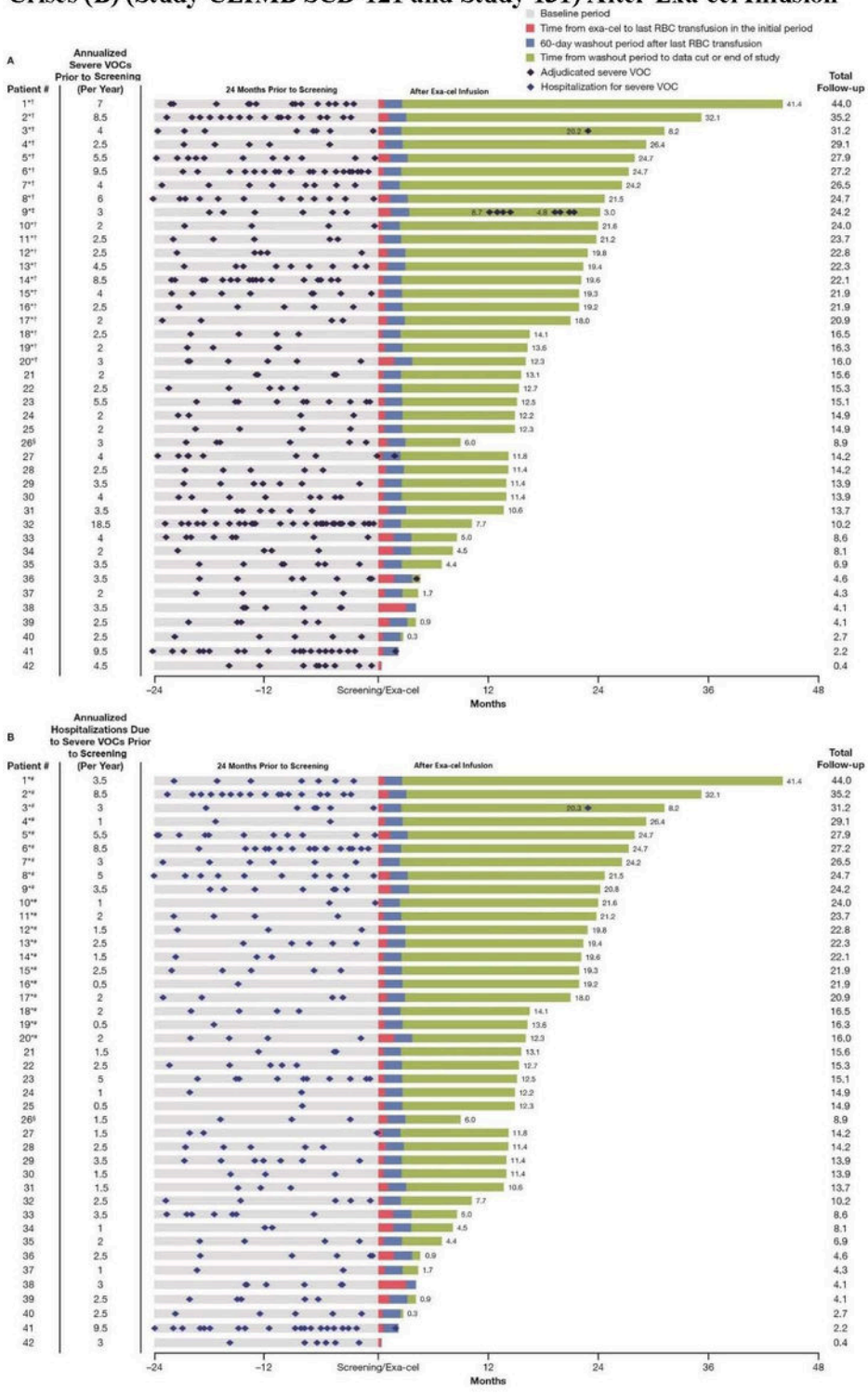
(95.0%) pts evaluable for primary endpoint were free of VOCs for ≥12 consecutive mos (VF12; 95% CI, 75.1% to 99.9%; P<0.0001), 20/20 (100%) were free from hospitalizations for VOCs for ≥12 consecutive mos (HF12; 95% CI, 83.2 to 100.0; P<0.0001), and 29/30 (96.7%) were free of VOCs for ≥9 consecutive mos (VF9; 95% CI, 82.8 to 99.9; P<0.0001). In pts achieving VF12, VOC free duration was 21.8 (range 12.3-41.4) mos; 18 pts remained VOC free through follow-up and 1 pt had an adjudicated VOC in the setting of parvovirus infection ~22.8 mos after exa-cel; pt recovered fully and has since been VOC free (Fig). For all pts, total Hb was 12.1 g/dL at Month 3 and was maintained at ≥11.0 g/dL from Month 6 onward; HbF was 36.0% at Month 3 and was generally maintained at ≥ 40.0% from Month 6 onward with pancellular distribution (≥95% RBCs expressing HbF). Proportion of edited *BCL11A* alleles was stable over time in bone marrow CD34 $^{+}$ and peripheral blood nucleated cells. 36/39 pts with ≥60 days follow-up after last RBC transfusion (including those not yet evaluable) remained VOC free (up to 41.4 mos; Fig). Quality-of-life (QOL) measures showed clinically significant improvements from baseline.

All pts had ≥1 adverse event (AE), most were Grade 1 or 2; 40 (95.2%) pts had AEs of Grade 3 or 4 severity. Most common AEs were nausea (66.7%), stomatitis (61.9%), febrile neutropenia (52.4%), headache (52.4%), and vomiting (52.4%). Most AEs and serious AEs (SAEs) occurred within first 6 mos after infusion. No pts had SAEs considered related to exa-cel. As previously reported, 1 pt died from respiratory failure due to COVID-19 unrelated to exa-cel. There were no study discontinuations or malignancies.

Conclusions: The CLIMB SCD-121 trial met primary and key secondary endpoints, with exa-cel treatment resulting in early and sustained increases in Hb and HbF leading to elimination of VOCs in 95% of pts, elimination of inpatient hospitalization for VOCs in 100% of pts and improved QOL. Safety profile of exa-cel was generally consistent with myeloablative busulfan conditioning and autologous transplantation. These results show exa-cel has the potential to deliver a one-time functional cure to pts with severe SCD.

Disclosures Frangoul: *Editas Medicine:* Consultancy; *Rocket Pharmaceuticals:* Consultancy, Other: Member of DSMB for a study; *Jazz Pharmaceuticals:* Speakers Bureau; *Vertex Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Sharma:** *Editas Medicine:* Consultancy; *RCI BMT/NMDP:* Honoraria, Other: Clinical Trial Medical Monitor; *Medexus Inc:* Consultancy; *Vertex Pharmaceuticals:* Consultancy, Other: Clinical Trial Site PI; *Sangamo Therapeutics:* Consultancy; *CRISPR Therapeutics:* Other: Clinical Trial Site PI, Research Funding. **Mapara:** *Crispr/vertex:* Consultancy; *Incyte:* Consultancy; *Bluebird bio:* Consultancy. **Liem:** *Bluebird Bio:* Research Funding; *NIH/NHLBI:* Research Funding; *NIH/NCATS:* Research Funding; *Vertex:* Research Funding; *Editas:* Research Funding; *Global Blood Therapeutics:* Research Funding. **Telfer:** *Apopharma:* Other: Clinical trial activity, Speakers Bureau; *Terumo:* Speakers Bureau; *Pfizer:* Other: Advisory board; Clinical trial activity; Data monitoring committee; ; *Napp Pharmaceuticals:* Other: Clinical trial activity; *Celgene:* Other: Clinical trial activity; *Kyowa Kirin Limited:* Other: Investigator-led funding; *Novartis:* Other: Advisory board; Clinical trial activity; ; *bluebird bio:* Other: Advisory board; Investigator-led funding;. **Shah:** *Vertex:* Membership on an entity's Board of Directors or advisory committees. **Rondelli:** *Vertex:* Other: Steering Committee. **Meisel:** *Miltenyi Biotech:* Research Funding; *medac:* Consultancy, Research Funding, Speakers Bureau; *Gilead/KITE:* Research Funding; *Novartis:* Consultancy, Research Funding, Speakers Bureau; *CELGENE BMS:* Consultancy, Research Funding, Speakers Bureau; *Bluebird Bio:* Consultancy, Speakers Bureau; *CRISPR Therapeutics:* Consultancy, Research Funding, Speakers Bureau; *Vertex:* Consultancy, Research Funding, Speakers Bureau. **Lobitz:** *AddMedica:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Other: Patient Booklet and educational papers; *Global Blood Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Agios:* Membership on an entity's Board of Directors or advisory committees; *BlueBird Bio:* Membership on an entity's Board of Directors or advisory committees, Other: Lecture; *Vertex Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees, Other: Steering Committee; *German National Disease Management Program:* Other: Spokesperson for children and adolescents with sickle cell disease; *German National Treatment Guideline:* Other: Corresponding author of the treatment guideline for children and adolescents with sickle cell disease. **de Montalembert:** *Addmedica:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: ASH meeting 2022 support; *Novartis:* Membership on an entity's Board of Directors or advisory committees. **Steinberg:** *NIH:* Research Funding; *Fulcrum Therapeutics:* Consultancy; *ASH:* Other: Lecture at HEM ASH Whiteboard Symposium, Speakers Bureau; *Imara Therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Walters:** *Ensoma, Inc:* Consultancy; *Vertex Pharmaceuticals:* Consultancy; *BioChip Labs:* Consultancy, Other: Medical Director; *AllCells, Inc:* Consultancy, Other: Medical Director. **Bower:** *Vertex Pharmaceuticals:* Current Employment. **Imren:** *Vertex Pharmaceuticals:* Current Employment, Current holder of *stock options* in a privately-held company. **Simard:** *Vertex Pharmaceuticals:* Current Employment. **Xuan:** *Vertex Pharmaceuticals:* Current Employment. **Zhou:** *Vertex Pharmaceuticals:* Current Employment. **Morrow:** *Vertex Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *CRISPR Therapeutics:* Current Employment, Membership on an entity's Board of Directors or advisory committees. **Hobbs:** *Vertex Pharmaceuticals:* Current Employment. **Grupp:** *Cabaletta:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Allogene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Juno:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Cellectis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Adaptimmune:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *CBMG:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servier:* Research Funding; *Kite:* Research Funding; *Jazz:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Vertex:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding.

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. *Participant was evaluable for the primary endpoint (VF12) and first key secondary endpoint (HF12); †Participant achieved VF12; ‡Participant did not achieve VF12; §Death from respiratory failure due to COVID-19 infection; #Participant achieved HF12

Figure 1

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