ELSEVIER

Blood 142 (2023) 1053–1055

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

801.GENE THERAPIES

Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia

Franco Locatelli, MD PhD[1], Peter Lang, MD PhD[2], Selim Corbacioglu, MDPhD[3], Donna Wall, MD[4], Roland Meisel, MD[5], Amanda M Li, MD[6], Josu de La Fuente, PhD[7], Ami J. Shah, MD[8], Ben Carpenter, MD PhD[9], Janet L. Kwiatkowski, MD MSCE[10], Markus Mapara, MD[11], Robert I. Liem, MD[12], Maria Domenica Cappellini, MD[13], Mattia Algeri, MD[1], Antonis Kattamis, MDPhD[14], Sujit Sheth, MD[15], Stephan Grupp, MD PhD[16], Puja Kohli, MD MMSc[17], Daoyuan Shi, PhD[17], Leorah Ross, MD PhD[17], Yael Bobruff, PhD[17], Christopher Simard, MD[17], Lanju Zhang, PhD[17], Phuong Khanh Morrow, MD[18], William Hobbs, MD PhD[17], Haydar Frangoul, MD[19]

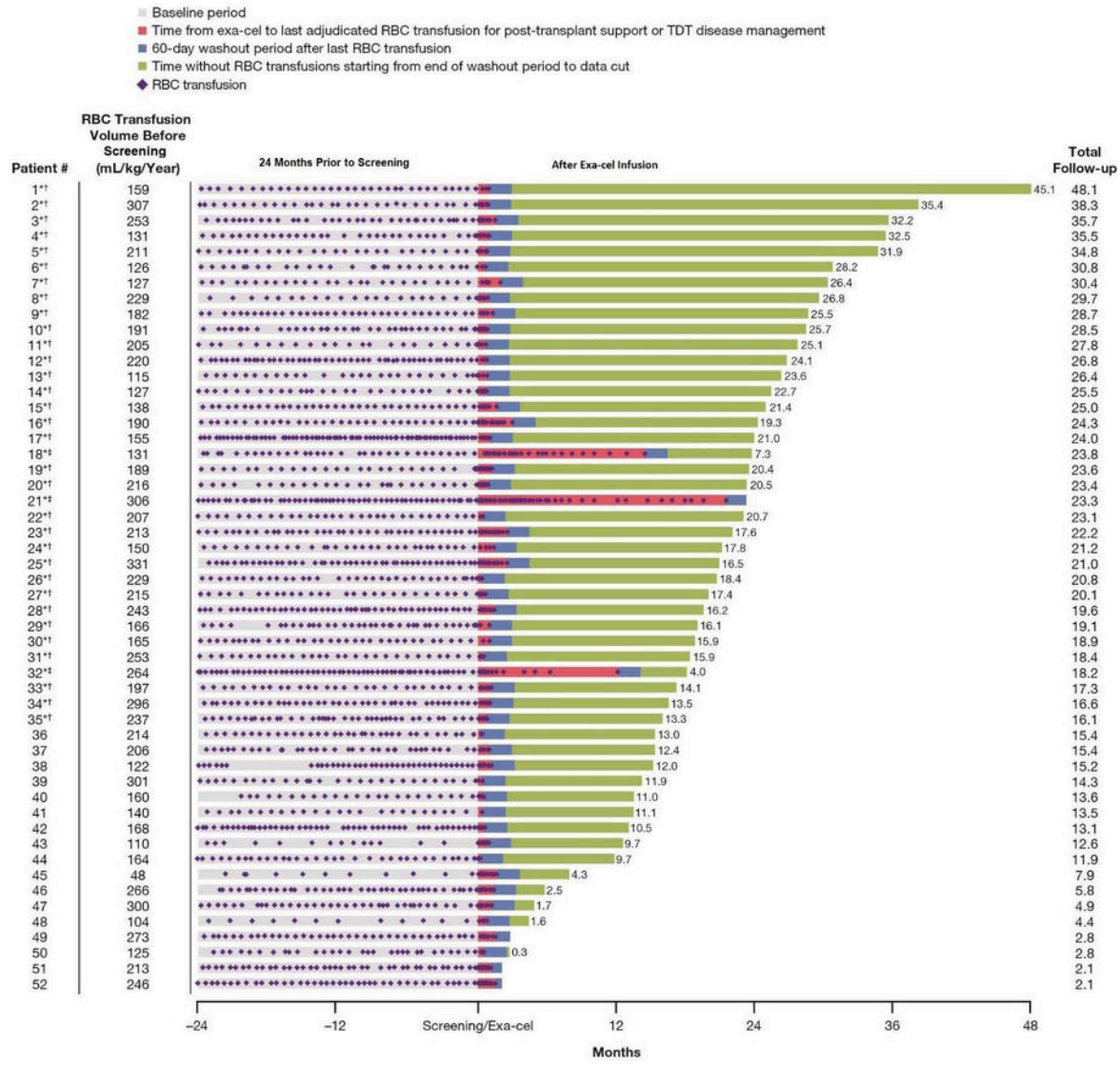
[1] IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Catholic University of the Sacred Heart, Rome, Italy
[2] University of Tübingen, Tübingen, Germany
[3] University of Regensburg, Regensburg, Germany
[4] The Hospital for Sick Children/University of Toronto, Toronto, Canada
[5] Division of Pediatric Stem Cell Therapy, Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany
[6] BC Children's Hospital, University of British Columbia, Vancouver, Canada
[7] Imperial College Healthcare NHS Trust, St Mary's Hospital, London, United Kingdom
[8] Center for Definitive and Curative Medicine, Stanford University, Palo Alto, CA
[9] University College London Hospitals NHS Foundation Trust, London, United Kingdom
[10] Children's Hospital of Philadelphia and Perlman School of Medicine, University of Pennsylvania, Philadelphia, PA
[11] Division of Hematology and Oncology, Columbia University, New York, NY
[12] Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL
[13] University of Milan, Milan, Italy
[14] National and Kapodistrian University of Athens, Athens, Greece
[15] Joan and Sanford I Weill Medical College of Cornell University, New York, NY
[16] Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
[17] Vertex Pharmaceuticals, Boston, MA
[18] CRISPR Therapeutics, Cambridge, MA
[19] Sarah Cannon Research Institute at The Children's Hospital at TriStar Centennial, Nashville, TN

Background: Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy designed to reactivate fetal hemoglobin (HbF) via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of BCL11A in patients (pts) with transfusion-dependent β-thalassemia (TDT). Here we report that in a pre-specified interim analysis, the pivotal CLIMB THAL-111 trial of exa-cel met primary and key secondary endpoints.
Methods: CLIMB THAL-111 is an ongoing, 24-month (mo), phase 3 trial of exa-cel in pts age 12-35y with TDT and a history of ≥100 mL/kg/y or ≥10 U/y packed red blood cell (RBC) transfusions in the 2y before screening. Primary endpoint is transfusion independence defined as proportion of pts maintaining a weighted average hemoglobin (Hb) ≥9 g/dL without RBC transfusion for ≥12 consecutive mos (TI12). Key secondary endpoint is proportion of pts maintaining a weighted average Hb ≥9 g/dL without RBC transfusion for ≥6 consecutive mos (TI6). Evaluable pts had ≥16 mos of follow-up after exa-cel infusion. Evaluation of TI12 and TI6 started 60 days after last RBC transfusion for post-transplant support or TDT management. Pts completing trial enrolled in long-term follow-up Study 131. Mean (SD) shown except where noted.
Results: As of 16 Jan 2023, 52 pts (mean age 21.5[range 12-35]y; 18[34.6%] age ≥12 to <18y; 31[59.6%] with severe genotypes [β^0/β^0 or β^0/β^0-like], median annualized transfusion volume 201.0 mL/kg) received exa-cel; median follow-up 20.4 (range 2.1-48.1) mos. Following infusion, all pts engrafted neutrophils and platelets (median 29 and 44 days, respectively). Of the 35 pts evaluable for primary and key secondary endpoints, 32 (91.4%) achieved TI12 and TI6 (95% CI: 76.9%, 98.2%; P<0.0001). Pts achieving TI12 stopped transfusions 35.2 (SD, 18.5) days after exa-cel infusion and remained transfusion independent for 22.5 (range, 13.3, 45.1) mos (Fig). For 3 pts not achieving TI12, one had reductions in annualized RBC transfusion volume of

83.9%, while the others have been transfusion-free for 7.3 mos and 4.0 mos starting 60 days after the last transfusion. For all pts, total Hb was 11.4 g/dL at Month 3 (≥12g/dL Month 6 onward) and HbF was 7.7 g/dL at Month 3 (≥ 10 g/dL Month 6 onward) with pancellular distribution (≥95% RBCs expressing HbF Month 6 onward). Proportion of edited *BCL11A* alleles was stable over time in bone marrow CD34 $^{+}$ and peripheral blood nucleated cells. Pts not yet evaluable and with sufficient follow-up were also transfusion-free. Quality-of-life (QOL) measures showed clinically significant improvements.
All pts had ≥1 adverse event (AE), most were Grade 1 or 2; 46 (88.5%) pts had AEs of Grade 3 or 4 severity. Most common AEs were febrile neutropenia (61.5%), headache (53.8%), and stomatitis (50.0%). Most AEs and serious AEs (SAEs) occurred within first 6 mos after infusion. Two pts had SAEs considered related to exa-cel: headache, hemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome and idiopathic pneumonia syndrome (latter also considered related to busulfan) all in the context of HLH (n=1) and delayed engraftment and thrombocytopenia (both also considered related to busulfan) (n=1), which all resolved. There were no deaths, discontinuations, or malignancies.
Conclusions: The CLIMB THAL-111 trial met primary and key secondary endpoints, with exa-cel treatment resulting in early and sustained increases in Hb and HbF leading to transfusion independence in >90% of pts with TDT 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 TDT.

Disclosures Meisel: *Gilead/KITE:* Research Funding; *CELGENE BMS:* Consultancy, Research Funding, Speakers Bureau; *CRISPR Therapeutics:* Consultancy, Research Funding, Speakers Bureau; *Vertex:* Consultancy, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Research Funding, Speakers Bureau; *Miltenyi Biotech:* Research Funding; *Bluebird Bio:* Consultancy, Speakers Bureau; *medac:* Consultancy, Research Funding, Speakers Bureau. **Shah:** *Vertex:* Membership on an entity's Board of Directors or advisory committees. **Carpenter:** *Vertex Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *BlueBird Bio:* Membership on an entity's Board of Directors or advisory committees. **Kwiatkowski:** *Regeneron Pharmaceuticals:* Consultancy; *Bristol Myers Squibb:* Consultancy; *BioMarin Pharmaceutical:* Consultancy; *Vertex Pharmaceuticals:* Consultancy; *Forma Therapeutics:* Consultancy, Research Funding; *Chiesi Farmaceutici:* Consultancy; *Bluebird Bio:* Research Funding; *Agios Pharmaceuticals:* Consultancy, Research Funding; *Editas Medicine:* Research Funding; *Pfizer:* Research Funding. **Mapara:** *Crispr/vertex:* Consultancy; *Incyte:* Consultancy; *Bluebird bio:* Consultancy. **Liem:** *Bluebird Bio:* Research Funding; *Vertex:* Research Funding; *NIH/NCATS:* Research Funding; *NIH/NHLBI:* Research Funding; *Editas:* Research Funding; *Global Blood Therapeutics:* Research Funding. **Algeri:** *Vertex Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Kattamis:** *Agios Pharmaceuticals:* Consultancy; *Bristol Myers Squib/Celegene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Vertex Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Chiesi:* Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Amgen:* Consultancy; *Ionis Pharmaceuticals:* Consultancy; *Vifor:* Consultancy. **Sheth:** *Agios:* Consultancy, Other: Travel support, Research Funding; *Bristol Myers Squibb/ Celegene:* Consultancy, Other: Travel support, Research Funding; *Bluebird bio:* Consultancy, Other: Travel support; *Fulcrum:* Consultancy; *Chiesi:* Consultancy; *CRISPR:* Membership on an entity's Board of Directors or advisory committees; *Vertex Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees. **Grupp:** *Novartis:* Consultancy, Research Funding; *Vertex:* Consultancy, Research Funding; *Jazz:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Kite:* Research Funding; *Servier:* Research Funding; *CBMG:* 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; *Cellectis:* 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; *Allogene:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Cabaletta:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Kohli:** *Vertex Pharmaceuticals:* Current Employment. **Shi:** *Vertex Pharmaceuticals:* Current Employment. **Ross:** *Vertex Pharmaceuticals:* Current Employment. **Bobruff:** *Vertex Pharmaceuticals:* Current Employment; *CRISPR Therapeutics, Inc:* Ended employment in the past 24 months. **Simard:** *Vertex Pharmaceuticals:* Current Employment. **Zhang:** *Vertex Pharmaceuticals:* Current Employment. **Morrow:** *CRISPR Therapeutics:* Current Employment, Membership on an entity's Board of Directors or advisory committees; *Vertex Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees. **Hobbs:** *Vertex Pharmaceuticals:* Current Employment. **Frangoul:** *Vertex Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Editas Medicine:* Consultancy; *Jazz Pharmaceuticals:* Speakers Bureau; *Rocket Pharmaceuticals:* Consultancy, Other: Member of DSMB for a study.

Figure 1. Duration of Period Free from Transfusions after Exa-cel Infusion (Study CLIMB THAL-111 and Study 131).



Exa-cel: exagamglogene autotemcel; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia

All RBC transfusions that occurred after exa-cel dosing were adjudicated by the Independent Endpoint Adjudication Committee. The washout period refers to the 60 days after the last RBC transfusion for post-transplant support or TDT management. The number to the right of the light green row is the duration of period free from RBC transfusions, starting 60 days after the last RBC transfusion. *Participant was evaluable for the primary endpoint; †Participant achieved TI12; ‡Participant did not achieve TI12

Figure 1

https://doi.org/10.1182/blood-2023-190534