(PS2333) LONG-TERM FOLLOW-UP CONFIRMS DURABLE CLINICAL BENEFITS OF EXAGAMGLOGENE AUTOTEMCEL IN TRANSFUSION-DEPENDENT B-THALASSEMIA: FINAL RESULTS OF THE CLIMB THAL-111 STUDY

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

Roland Meisel*[1], Haydar Frangoul[2], Selim Corbacioglu[3], Josu De La Fuente[4], Peter Lang[5], Mattia Algeri[6], Joachim Rupprecht[5], Kevin H.M. Kuo[7], Melanie Kirby-Allen[8], Amanda M. Li[9], Ami J. Shah[10], Markus Mapara[11], Ben Carpenter[12], Robert Liem[13], Janet L. Kwiatkowski[14], Hayley Merkeley[15], Stephan Grupp[14], Maria Domenica Cappellini[16], Antonis Kattamis[17], Sujit Sheth[18], Kathleen Lee-Sarwar[19], Bo Tong[19], Sakellarios Zairis[19], William Hobbs[19], Franco Locatelli[20]

[1]Heinrich-Heine-University, Division of Pediatric Stem Cell Therapy, Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Düsseldorf, Germany; [2]Sarah Cannon Research Institute at The Children's Hospital at TriStar Centennial, Nashville, United States of America; [3]University of Regensburg, Regensburg, Germany; [4]Imperial College Healthcare NHS Trust, St Mary's Hospital, London, United Kingdom; [5]University of Tübingen, Tübingen, Germany; [6]IRCCS, Ospedale Pediatrico Bambino Gesù, Rome, Italy; [7]University of Toronto, Division of Hematology, Toronto, Canada; [8]Hospital for Sick Children, Toronto, Canada; [9]BC Children's Hospital, University of British Columbia, Vancouver, Canada; [10]Stanford University, Palo Alto, United States of America; [11]Columbia University, Division of Hematology and Oncology, New York, United States of America; [12]University College London Hospitals NHS Foundation Trust, London, United Kingdom; [13]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, United States of America; [14]Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, United States of America; [15]The University of British Columbia/Adult Red Cell Disorder Program of British Columbia, Department of Medicine, Vancouver, Canada; [16]University of Milan, Milan, Italy; [17]National and Kapodistrian University of Athens, Athens, Greece; [18]Joan and Sanford I Weill Medical College of Cornell University, New York, United States of America; [19]Vertex Pharmaceuticals Incorporated, Boston, United States of America; [20]IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Catholic University of the Sacred Heart, Rome, Italy;

Background

Exagamglogene autotemcel (exa-cel) is a one-time, non-viral, *ex vivo* CRISPR/Cas9 gene-edited, autologous cell therapy approved for patients ≥12 years old with transfusion-dependent β-thalassemia (TDT).

Aims

Evaluate longer-term efficacy and safety of exa-cel in TDT participants aged 12 to 35 years and provide final study results of the CLIMB THAL-111 trial.

Methods

CLIMB THAL-111 is a 2-year, Phase 3 study of exa-cel in TDT participants aged 12 to 35 years. The primary endpoint is transfusion independence defined as proportion of participants maintaining a weighted average hemoglobin (Hb) ≥9 g/dL without RBC transfusion for ≥12 consecutive months (TI12). CLIMB-111 participants then enroll in long-term follow-up study CLIMB-131 for up to 15 years of follow-up after exa-cel infusion. Measures of tissue iron overload (serum ferritin, liver iron concentration [LIC], and T2* cardiac iron content [CIC]) and measures of iron homeostasis (e.g., erythroferrone and hepcidin) were assessed after exa-cel, including data collected before and after discontinuation of iron removal therapy (IRT; namely chelation and/or phlebotomy). Patient-reported outcomes (PROs) were also assessed. Data are from 20 July 2025; data will be updated to reflect the final results from the completed CLIMB THAL-111 trial.

Results

56 participants (mean age: 21.2 years [range: 12, 35]) received exa-cel in CLIMB THAL-111 and had median follow-up of 4.1 years (range: 1.6, 6.6). 35/56 participants (62.5%) had severe genotypes (β^0/β^0 or β^0/β^0-like). Median number of mobilization cycles was 1 (range: 1, 4); the mean number of cells infused was 8.4 (range: 3.0, 19.7) × 10^6 cells/kg. After exa-cel infusion, 98.2% (55/56) achieved TI12 in CLIMB-THAL-111 and CLIMB-131 combined, with a median duration of transfusion independence of 3.9 years (range: 1.4, 6.3). Mean total Hb was maintained at normal/near normal levels of ≥12 g/dL and mean HbF, with pancellular distribution, was ≥11 g/dL from Month 6 onward. Allelic editing in both bone marrow and peripheral blood was stable over time. In CLIMB THAL-111 and CLIMB-131 combined, all participants received IRT after exa-cel with 69.6% (39/56) discontinuing IRT for ≥6 months. After IRT discontinuation, levels of serum ferritin, LIC, and CIC were generally stable without progressive increase for over 5 years. Erythroferrone and hepcidin levels also remained stable after IRT discontinuation at levels consistent with normalization of iron homeostasis and correction of ineffective erythropoiesis after exa-cel. In addition, durable improvements in PROs after exa-cel were observed in both adults and adolescents.
Exa-cel safety was consistent with myeloablative conditioning and autologous transplant. There were no deaths or malignancies through follow-up in both CLIMB THAL-111 and CLIMB-131.

Summary/Conclusion

Exa-cel demonstrated durable clinical benefits in adults and adolescents with TDT for up to 6.5 years of follow-up. In addition to durable transfusion independence in 98.2% of participants, there was no evidence of iron reaccumulation after IRT discontinuation. This suggests that, in addition to transfusion independence, exa-cel also has the potential to prevent tissue iron accumulation via correction of underlying ineffective erythropoiesis. The safety profile is consistent with busulfan myeloablative conditioning and autologous transplant. These data continue to support exa-cel as a potential one-time functional cure for TDT.