Reni-cel, the first AsCas12a gene-edited cell therapy, shows promising preliminary results in key clinical outcomes in transfusion-dependent β-thalassemia patients treated in the EdiThal trial

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H. Frangoul[1], R. Hanna[2], M.C. Walters[3], K. Chang[4], M. Jaskolka[4], K. Kim[4], B. Mei[4], O. Afonja[4], A. Thompson[5]

[1]Sarah Cannon Research Institute at the Children's Hospital at TriStar Centennial, Nashville, TN, USA; [2]Department of Pediatric Hematology Oncology and Blood and Marrow Transplantation, Cleveland Clinic, Cleveland, OH, USA; [3]University of California, San Francisco Benioff Children's Hospital, Oakland, CA, USA; [4]Editas Medicine, Inc., Cambridge, MA, USA; [5]Children's Hospital of Philadelphia, Philadelphia, PA, USA.

INTRODUCTION

- Transfusion-dependent β-thalassemia (TDT) is a hereditary blood disorder caused by reduced or absent production of β-globin.[1]
- Clinical evidence has demonstrated that increased fetal hemoglobin (HbF, α2γ2) can lead to durable transfusion independence, reduced disease severity, and improved quality of life for patients with TDT.[2,3]
- Renizgamglogene autogedtemcel (reni-cel) is an investigational gene-edited autologous hematopoietic stem cell medicine comprised of CD34$^+$ cells from patients that are edited at the γ-globin gene (*HBG1* and *HBG2*) promoters to induce HbF expression.
- These edits mimic naturally occurring variants of hereditary persistence of HbF in the *HBG1* and *HBG2* promoters, resulting in reactivation of γ-globin expression and increased HbF production.[4]
- Reni-cel is manufactured with a highly efficient and specific, proprietary gene editing nuclease, *Acidaminococcus sp*. CRISPR-associated protein 12a (AsCas12a).
- In preclinical studies, editing of this genomic region at the *HBG1* and *HBG2* promoters in CD34$^+$ cells from patients with TDT led to improved erythropoiesis *in vitro* and erythroid progeny with increased total hemoglobin (Hb) production.[5]
- Here we report preliminary clinical data (as of May 8, 2024) on reni-cel efficacy and safety in patients with TDT.

METHODS

- EdiThal (NCT05444894) is a multi-center, open-label, single-arm Phase I/II study evaluating the safety, efficacy, and tolerability of reni-cel in patients with TDT.
- Key inclusion and exclusion criteria and primary endpoints are summarized in **Table 1**.
- Autologous CD34$^+$ hematopoietic stem and progenitor cells are collected by apheresis after plerixafor + filgrastim mobilization and edited at the *HBG1* and *HBG2* promoters with the highly efficient and specific, proprietary gene editing nuclease, AsCas12a.
- After myeloablative conditioning with busulfan, patients received a single infusion of reni-cel (a minimum of 3 × 10^6 CD34$^+$ cells/kg) and were monitored for engraftment, total Hb, HbF production, percentage of F-cells, transfusion requirement, and treatment-emergent adverse events (TEAEs) for 24 months.
- Data included here are based on a cutoff of May 8, 2024.

Table 1. Key eligibility criteria and primary endpoints for the EdiThal trial (NCT05444894)

Key inclusion criteria
• 18–35 years • Diagnosis of TDT • History of at least 100 mL/kg/year or 10 U/year of packed RBC transfusions in the 2 years prior to informed consent
Key exclusion criteria
• Available genetically-matched (10/10 HLA) related donor • Previous or current malignancy or immunodeficiency disorder • Unable to tolerate stem cell therapy or receive RBC transfusion
Primary endpoints
• Proportion of participants achieving neutrophil engraftment on or by 42 days post-reni-cel infusion • Safety and tolerability of reni-cel

HLA, human leukocyte antigen; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel; TDT, transfusion-dependent β-thalassemia; U, units.

RESULTS

Table 2. Patient demographics and baseline characteristics

Demographics and baseline characteristics	(N=7)
Genotype, n (%)	
β^0/β^0 or β^0/β^0-like*	3 (42.9)
Non-β^0/β^0†	4 (57.1)
Sex, n (%)	
Female	4 (57.1)
Age, years, median (min, max)	19.0 (18.0, 24.0)
Packed RBC transfusions, pre-study annual rate‡, mL/kg/year, mean (SD)	153.5 (52.9)

*β^0/β^0-like includes IVS-I-110/ IVS-I-110 (n=1).
†Non-β^0/β^0 includes β^0/β$^+$ (n=3) and β^E/β^0 (n=1).
‡The pre-study period is defined as the 2-year period prior to informed consent.
IVS, intervening sequence; max, maximum; min, minimum; RBC, red blood cell; SD, standard deviation.

Table 3. Seven patients have received reni-cel infusion and all successfully engrafted

Parameter	(N=7)
Mobilization and apheresis cycles	
No. of cycles, median (min, max)	1.0 (1.0, 1.0)
Reni-cel infusion	
Total reni-cel dose administered, × 10^6 CD34$^+$ cells/kg, median (min, max)	6.7 (5.7, 11.9)
Follow-up duration, months, median (min, max)	8.8 (4.7, 13.4)
Engraftment	
Time to neutrophil engraftment*, days, median (min, max)	23.0 (16.0, 30.0)
Time to platelet engraftment†, days, median (min, max)	38.0 (24.0, 49.0)

- High levels of editing were observed after reni-cel infusion.
  - At Month 6, mean (SD) editing levels were 75.4% (5.3%) in patient peripheral blood nucleated cells (n=6) and 79.9% (9.1%) in patient bone marrow–derived CD34$^+$ cells (n=4).

*Three consecutive measurements with absolute neutrophil count (ANC) ≥0.5 × 10^9/L.
†Three consecutive measurements with platelet count ≥20 × 10^9/L starting at least 7 days after the platelet transfusion and 10 days after thrombopoietin.
Max, maximum; min, minimum; reni-cel, renizgamglogene autogedtemcel; SD, standard deviation.

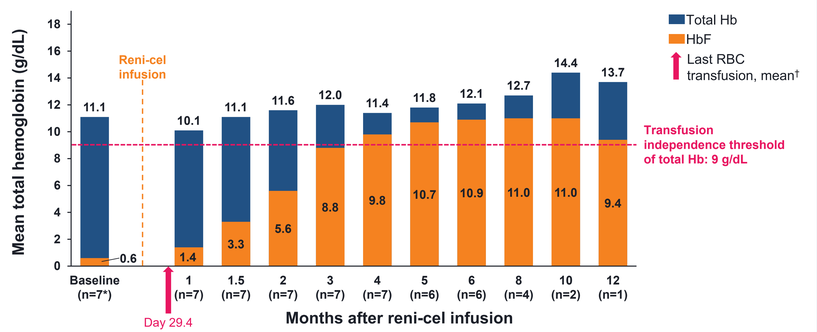
Table 4. The safety profile of reni-cel in patients with TDT was consistent with myeloablative conditioning with busulfan and autologous HSCT

TEAE category	(N=7)	
	No. of patients (%)	No. of events
Any TEAE	7 (100.0)	155
Any TEAE related to reni-cel*	1 (14.3)	2
Any TEAE related to busulfan	7 (100.0)	112
Any serious TEAE†	3 (42.9)	3
Any serious TEAE related to reni-cel	0	0
Any Grade 3 or 4 TEAE	7 (100.0)	57
Any Grade 3 or 4 TEAE related to reni-cel	1 (14.3)	1
Any TEAE related to reni-cel leading to discontinuation	0	0
Any TEAE leading to death	0	0

- No serious TEAEs related to reni-cel were reported.

*One patient experienced 2 non-serious TEAEs (Grade 2 CD4 lymphocytes decreased, and Grade 3 lymphocyte count decreased), which were reported to be causally related to reni-cel and busulfan. Both TEAEs are ongoing as of the data cutoff date.
†Serious TEAEs were COVID-19, device-related infection, and pneumonitis.
HSCT, hematopoietic stem cell transplantation; reni-cel, renizgamglogene autogedtemcel; TDT, transfusion-dependent β-thalassemia; TEAE, treatment-emergent adverse event.

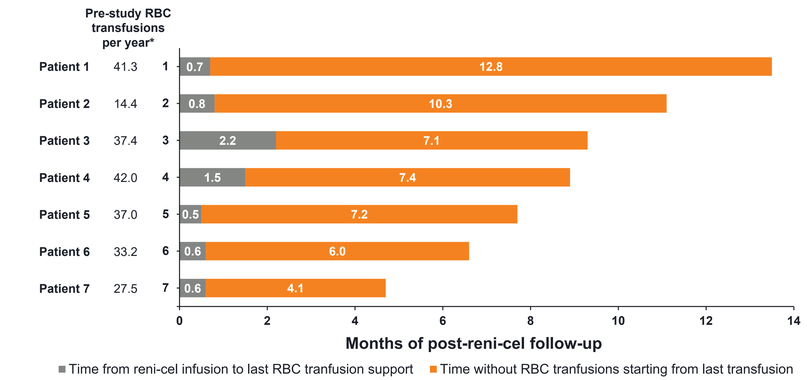
Figure 1. Following reni-cel infusion, mean total Hb and HbF increased



- All patients maintained Hb levels above the transfusion threshold at last follow-up.
- The mean (SD) HbF concentration increased early and was 10.9 (1.5) g/dL by Month 6 (n=6).
- The mean (SD) percentage of F-cells was 99.2% (0.8%) by Month 6 (n=5).

Bars show Hb (g/dL). Labels inside/next to the bars indicate mean levels of HbF (g/dL). Mean total Hb concentrations are shown directly above bars (g/dL). *At baseline n=6 for HbF. †The last RBC transfusion in patients occurred a mean (SD) of 29.4 (19.1) days after reni-cel infusion (n=7).
Hb, hemoglobin; HbF, fetal hemoglobin; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel; SD, standard deviation.

Figure 2. Patients have been transfusion-free for up to 12.8 months after reni-cel infusion



- After receiving the last RBC transfusion at 0.5–2.2 months post-reni-cel infusion, all 7 patients have been transfusion free for a range of 4.1–12.8 months.

Labels inside bars indicate number of months. *Number of transfusion units annualized over 2 years.
RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel.

CONCLUSIONS

- Reni-cel, the first investigational AsCas12a gene-edited therapy, showed promising results for gene editing of the γ-globin gene (*HBG1* and *HBG2*) promoters to induce HbF expression in patients with TDT.
- All patients maintained Hb levels above the transfusion threshold and have been transfusion free for up to 12.8 months after reni-cel infusion.
- All patients experienced early increases in HbF, with sustained HbF levels at or near the transfusion threshold from 6 months onward.
- These data demonstrate successful engraftment and a safety profile that is consistent with myeloablative busulfan conditioning and autologous hematopoietic stem cell transplantation.
- These findings from treated patients with TDT of longer duration build on strong clinical evidence that support the ongoing investigation of reni-cel in the EdiThal clinical trial.

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