Reni-cel, an Investigational AsCas12a Gene-Edited Cell Medicine, Led to Successful Engraftment, Increased Hemoglobin, and Reduced Transfusion Dependence in Patients with Transfusion-Dependent Beta-Thalassemia Treated in the EdiThal Trial

345

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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]
- **OBJECTIVES:** The EdiThal trial (NCT05444894), a Phase I/II, multicenter, open-label, single-arm study is evaluating the safety, tolerability, and efficacy of reni-cel in patients with TDT. Interim clinical data on safety and efficacy are reported

METHODS

- 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 a 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 November 12, 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 after 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=9)
Genotype, n (%)	
β^0/β^0* or β^0/β^0-like*	4 (44.4)
Non-β^0/β^{0†}	5 (55.6)
Sex, n (%)	
Male	5 (55.6)
Age, years, median (min, max)	20.0 (18.0, 29.0)
Race, n (%)	
Asian	7 (77.8)
White	2 (22.2)
Packed RBC transfusions, pre-study annual rate,‡ mL/kg/year, mean (SD)	145.7 (50.2)

*β^0/β^0-like includes IVS-I-110 / IVS-I-110 (n=1). †Non-β^0/β^0 includes β^0/β$^+$ (n=4) 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; RBC, red blood cell; SD, standard deviation.

Table 3. Reni-cel treatment characteristics

Parameter	(N=9)
Mobilization and apheresis cycles	
No. of cycles, median (min, max)	1.0 (1.0, 4.0)
Reni-cel infusion	
Total reni-cel dose administered, × 10^6 CD34$^+$ cells/kg, median (min, max)	6.1 (3.3, 11.9)
Follow-up duration, months, median (min, max)	14.0 (0.3, 19.9)
Engraftment (N=8)*	
Time to neutrophil engraftment,† days, median (min, max)	23.5 (16.0, 30.0)
Time to platelet engraftment,‡ days, median (min, max)	37.5 (23.0, 49.0)

- High levels of editing were observed after reni-cel infusion.
  - At Month 6, mean (SD) editing levels were 75.7% (4.9%) in patient peripheral blood nucleated cells (n=7) and 79.9% (7.1%) in patient bone marrow–derived CD34$^+$ cells (n=6).

*Engraftment evaluable in eight patients. †Three consecutive measurements with ANC ≥0.5 × 10^9/L. Based on eight patients who achieved neutrophil engraftment by the time of the data cutoff date. ‡Three consecutive measurements with platelet count ≥20 × 10^9/L starting at least 7 days after the platelet transfusion and 10 days after thrombopoietin. Based on eight patients who achieved platelet engraftment by the time of the data cutoff date.
ANC, absolute neutrophil count; reni-cel, renizgamglogene autogedtemcel; SD, standard deviation.

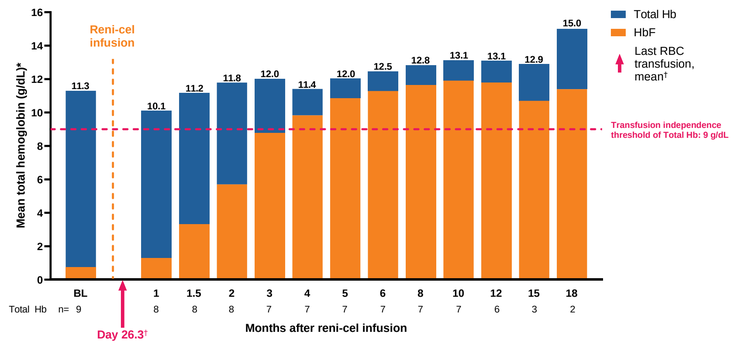
Table 4. The safety profile of reni-cel was consistent with myeloablative conditioning with busulfan and autologous HSCT

TEAE category	(N=9)	
	No. of patients (%)	No. of events
Any TEAE	8 (88.9)	172
Any TEAE related to reni-cel*	1 (11.1)	2
Any TEAE related to busulfan	8 (88.9)	121
Any serious TEAE†	3 (33.3)	3
Any serious TEAE related to reni-cel	0	0
Any Grade 3 or 4 TEAE	8 (88.9)	63
Any Grade 3 or 4 TEAE related to reni-cel	1 (11.1)	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 two non-serious TEAEs (Grade 2 and Grade 3 lymphocyte count decreased), which were reported to be causally related to reni-cel and busulfan. As of cutoff date, Grade 3 lymphocyte count decrease was resolved and Grade 2 lymphocyte decrease was ongoing. †Serious TEAEs were COVID-19, device-related infection, and pneumonitis.
HSCT, hematopoietic stem cell transplantation; reni-cel, renizgamglogene autogedtemcel; TEAE, treatment-emergent adverse event.

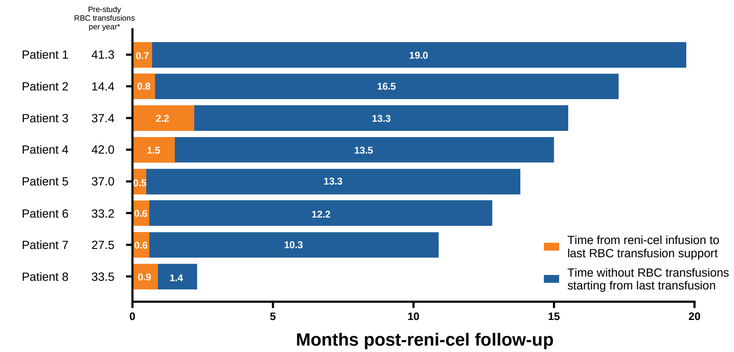
Figure 1. Following reni-cel infusion, mean total Hb and HbF increased



- All patients with >1 month follow-up maintained Hb levels above the transfusion threshold at last visit.
- The mean (SD) HbF concentration increased early and was 11.3 (1.7) g/dL by Month 6 (n=7).
- The mean (SD) percentage of F-cells was 99.2% (0.7%) by Month 6 (n=6).

Bars show Hb (g/dL). Mean total Hb concentrations are shown directly above bars (g/dL). *At baseline n=8 for HbF. †The last RBC transfusion in patients occurred a mean (SD) of 26.3 (18.7) days after reni-cel infusion (n=9).
BL, baseline; 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 19.0 months after reni-cel infusion



- After receiving the last RBC transfusion at 0.5–2.2 months after reni-cel infusion (n=8), all eight patients with >1 month follow-up have been transfusion free for a range of 1.4–19.0 months.

Labels inside bars indicate number of months. *Number of transfusion units annualized over 2 years. Only patients with >1 month of follow-up are included.
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 with >1 month of follow-up maintained Hb levels above the transfusion threshold and were transfusion free for up to 19.0 months after reni-cel infusion.
- Patients also experienced early and sustained increases in HbF, with normal or near normal levels of Hb from Month 6.
- These data demonstrate successful engraftment and a safety profile that is consistent with myeloablative busulfan conditioning and autologous hematopoietic stem cell transplantation.

REFERENCES

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