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TANDEM MEETINGS

Transplantation & Cellular Therapy Meetings *of* ASTCT® and CIBMTR®

February 12-15, 2025

Hawai‘i Convention Center, Honolulu, HI

Reni-Cel, an Investigational AsCas12a Gene-Edited Cell Medicine, Led to Sustained Hemoglobin Normalization and Increased Fetal Hemoglobin in Patients with Severe Sickle Cell Disease Treated in the RUBY Trial

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2025 Tandem Meetings Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®, Honolulu, Hawai'i, February 12–15, 2025

Disclosure slide

Mark Walters, MD

- Sanofi – Consultant, received honorarium. This relationship has ended.
- Vertex Pharmaceuticals – Advisory committee member, received consulting fee. This is a current financial relationship.
- Ensoma – Scientific board member, received consulting fee. This is a current financial relationship.

Sickle cell disease is a life-threatening hematological disorder

SCD is a genetic blood disorder caused by variants in the ***HBB* gene**, which cause **RBCs** to **sickle**[1,2]

Progressive multi-organ damage, adverse events, and comorbidities **reduce quality of life and shorten lifespan**[1–4]

There is an **unmet need** for broadly accessible transformative treatments for **patients with SCD** who lack an HLA-matched donor[4,5]

Sustained increases in levels of hemoglobin and fetal hemoglobin have positive clinical benefits:

Hemoglobin

Sustained hemoglobin concentration at the normal physiological range **reduces** risk for **end-organ damage** and other **negative outcomes** in patients with SCD[6]

Fetal hemoglobin

Increased fetal hemoglobin correlates with **reduction** or **elimination** of SCD **symptoms**, including VOEs[7–10]

HBB, β-globin gene; HLA, human leukocyte antigen; RBC, red blood cell; SCD, sickle cell disease; VOE, vaso-occlusive event.

1. Royal CDM *et al. Adv Genet (Hoboken)* 2021; 2(1): e10037. 2. Modell B *et al*. *Bull World Health Organ* 2008; 86 (6): 480–487. 3. Dampier C *et al. Am J Hematol* 2011; 86 (2): 203–205. 4. Kato GJ *et al. Nat Rev Dis Primers* 2018; 4: 18010. 5. Gupta *AO et al. Cytotherapy* 2024; 26 (11): 1411–1420. 6. Ershler WB *et al. Curr Ther Res Clin Exp* 2023; 98: 100696. 7. Powars DR *et al. Blood* 1984; 63 (4): 921–926. 8. Charache S *et al. N Engl J Med* 1995; 332 (20): 1317–1322. 9. Frangoul H *et al. N Engl J Med* 2024; 390 (18): 1649–1662. 10. Forget *BG. Ann N Y Acad Sci* 1998; 850: 38–44.

Reni-cel employs AsCas12a editing of *HBG1* and *HBG2* promoter regions to induce HbF

Renizgamglogene autogedtemcel (reni-cel) is an investigational gene-edited autologous hematopoietic stem cell medicine

Utilizing proprietary **AsCas12a** designed to edit with high efficiency and minimize off-target effects[1]

Targets both ***HBG1 and HBG2*** promoter regions to mimic naturally occurring HPFH[2]

Reni-cel mechanism of action in SCD

α, α-globin; β, β-globin; β^S, sickle β-globin; γ, γ-globin; AsCas12a, *Acidaminococcus* sp. Cas12a; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; HbF, fetal hemoglobin; *HBG*, γ-globin gene; HbS, sickle hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease.

1. Zhang L *et al*. *Nat Commun* 2021; 12 (1): 4500. 2. Canver MC *et al*. *Blood* 2016; 127 (21): 2536–2545.

The RUBY trial is designed to evaluate the safety, tolerability, and efficacy of reni-cel in patients with severe SCD

Design

- Phase I/II
- International, multicenter
- Open-label, single-arm study
- 24 months of follow-up post-reni-cel infusion

Key inclusion criteria

- 12–50 years
- Diagnosis of severe SCD*
- History of ≥2 severe VOEs† per year in previous 2 years

Key exclusion criteria

- Available 10/10 HLA–matched related donor
- Previous or current malignancy or immunodeficiency disorder
- Unable to tolerate stem cell therapy or receive RBC transfusion

Key endpoints

- Proportion of patients achieving complete resolution of severe VOEs†
- Safety and tolerability of reni-cel

*β^S/β^S, β^S/β^0, β^S/β^+, $\beta^S\beta^D$, $\beta^S\beta^{OArab}$. †A severe VOE requiring medical attention (despite hydroxyurea or other supportive care measures in the pre-treatment period) is defined as: an acute episode of pain with no cause other than a vaso-occlusion, resulting in either a ≥24-h hospital or ER observation unit or ≥2 visits to a day unit or ER over 72 h with both visits requiring administration of pain medications; acute priapism lasting >2 h and requiring a visit to a medical facility (with or without hospitalization); ACS, which is defined as chest-wall pain in association with findings of a new pulmonary infiltrate on chest X-ray films associated with fever and/or respiratory symptom; or hepatic or splenic sequestration, which is defined as a sudden increase in organ size associated with pain in the area of the organ, decrease in the hemoglobin concentration of ≥2 g/dL within a 24-h period, and, for liver sequestration, abnormal change in liver function tests, including conjugated bilirubin, not due to biliary tract disease.

β, β-globin allele; β^S, sickle β-globin; ACS, acute chest syndrome; ER, emergency room; h, hour; HLA, human leukocyte antigen; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; VOE, vaso-occlusive event.

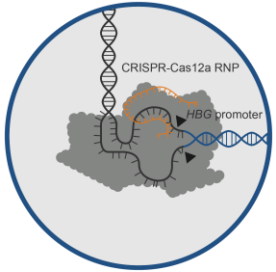
ClinicalTrials.gov NCT04853576. Available at: https://clinicaltrials.gov/ct2/show/NCT04853576. Accessed January 2025.

RUBY trial participants are monitored for 24 months after a single infusion of reni-cel

SCREENING → MOBILIZATION & APHERESIS → DRUG PRODUCT MANUFACTURING → MYELOABLATION & RENI-CEL INFUSION → ENGRAFTMENT & 24 MONTH FOLLOW-UP

Obtain consent and screen patients

HSPC mobilization and apheresis



CD34⁺ cells edited at *HBG1* and *HBG2* promoters with CRISPR-AsCas12a

Myeloablative conditioning with busulfan and reni-cel drug product infusion

24-month follow-up for primary endpoint

AsCas12a, *Acidaminococcus* sp. Cas12a; Cas, CRISPR-associated protein; CD, cluster of differentiation; CRISPR, clustered regularly interspaced short palindromic repeats; *HBG*, γ-globin gene; HSPC, hematopoietic stem and progenitor cells; reni-cel, renizgamglogene autogedtemcel; RNP, ribonucleoprotein.

Editas Medicine. Data on file.

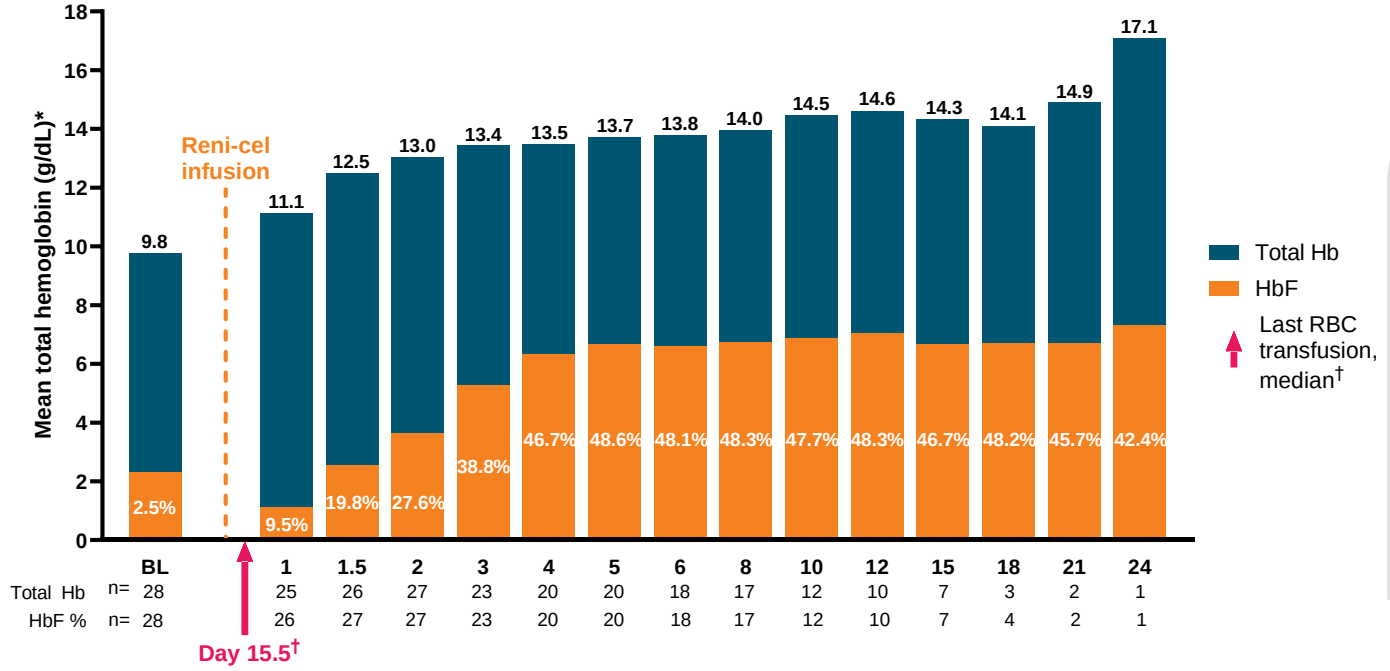
RUBY patient demographics, baseline characteristics, and treatment characteristics

DEMOGRAPHICS AND BASELINE CHARACTERISTICS	(N=28)
SCD genotype, n (%)	
β^S/β^S	27 (96.4)
Sex, n (%)	
Female	15 (53.6)
Race, n (%)	
Black or African American	27 (96.4)
Other	1 (3.6)
Age, years, mean (SD)	26.1 (5.75)
Severe VOEs, pre-study annual rate, mean* (SD)	4.6 (2.55)

MOBILIZATION, APHERESIS, INFUSION, AND ENGRAFTMENT	(N=28)
Number of mobilization and apheresis cycles,† median (range)	2.0 (1.0–4.0)
Total reni-cel dose administered, × 10^6 $CD34^+$ cells/kg, median (range)	4.3 (2.9–10.0)
Time to neutrophil engraftment,‡ days, median (range)	23.0 (14.0–29.0)‡
Time to platelet engraftment,§ days, median (range)	25.0 (17.0–51.0)§
Follow-up duration, months, median (range)	9.5 (0.7–25.2)

Data cutoff date: October 29th, 2024. *The pre-study period is defined as the 2-year period prior to informed consent. †Number of leukapheresis cycles for collection of sufficient cells for reni-cel manufacture. ‡Defined as three consecutive measurements with ANC ≥0.5 × 10^9/L. Based on 27 patients who had achieved neutrophil engraftment by the time of the data cut. §Defined as three consecutive measurements with platelet count ≥50 × 10^9/L starting at least 7 days after the platelet transfusion, and 10 days after TPO. No TPO was used for patients after reni-cel infusion. Based on 27 patients who had achieved platelet engraftment by the time of the data cut.
β^S, sickle β-globin; ANC, absolute neutrophil count; CD, cluster of differentiation; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; SD, standard deviation; TPO, thrombopoietin; VOE, vaso-occlusive event.

Early, durable correction of anemia with sustained HbF induction were observed after reni-cel infusion

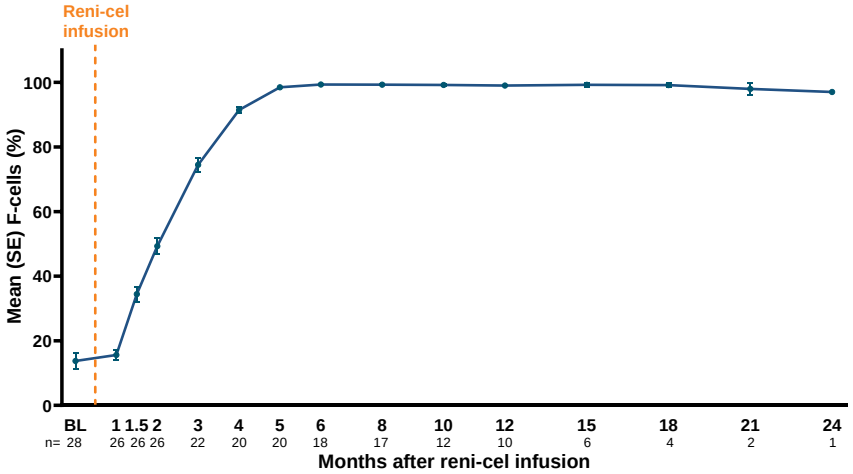


Markers of hemolysis, including absolute reticulocyte count, indirect bilirubin, lactate dehydrogenase, and haptoglobin were stably improved or normalized by Month 6

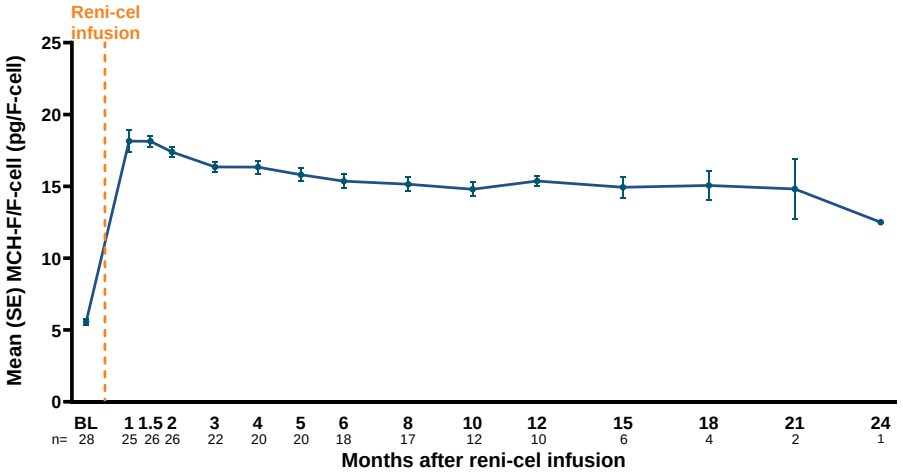
Data cutoff date: October 29th, 2024. Total number of female patients = 15; total number of male patients = 13. Bars show mean Hb (g/dL). Labels inside bars indicate mean proportion of HbF as a percentage of total Hb. Mean total Hb concentrations are shown above bars and the corresponding number of patients (n) are shown below. Not all patients had an evaluable sample at each timepoint. *Central laboratory reference range: 12.0–16.0 g/dL for females and 13.6–18.0 g/dL for males. †The last RBC transfusion occurred a median (range) of 15.5 (2.0–35.0) days after reni-cel infusion (n=26).
BL, baseline; Hb, hemoglobin; HbF, fetal hemoglobin; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel.

Increased percentage of F-cells and MCH-F/F-cell were observed early and were durable

By Month 6 (n=18), mean (SD) percentage of F-cells had increased to 99.3% (0.9%) and levels were maintained at >97% through last follow-up



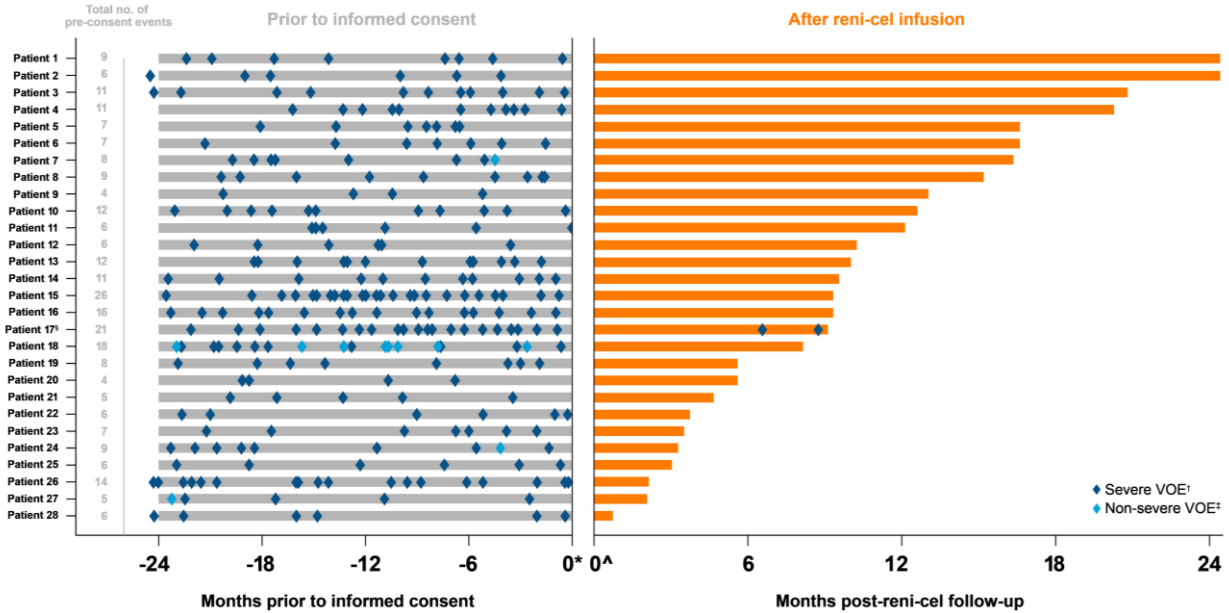
Mean MCH-F/F-cell increased early and was maintained above the anti-sickling threshold of 10 pg/F-cell through last follow-up



Patients showed sustained high levels of allelic editing in both peripheral blood nucleated cells and bone marrow–derived CD34^{+} cells, with mean (SD) editing levels of 75.1% (10.8% [n=8]) and 87.8% (3.4% [n=7]) at Month 12, respectively

Data cutoff date: October 29th, 2024. BL, baseline; CD, cluster of differentiation; F-cell, red blood cell expressing fetal hemoglobin; MCH-F/F-cell, mean corpuscular fetal hemoglobin per F-cell; reni-cel, renizgamglogene autogedtemcel; SD, standard deviation; SE, standard error.

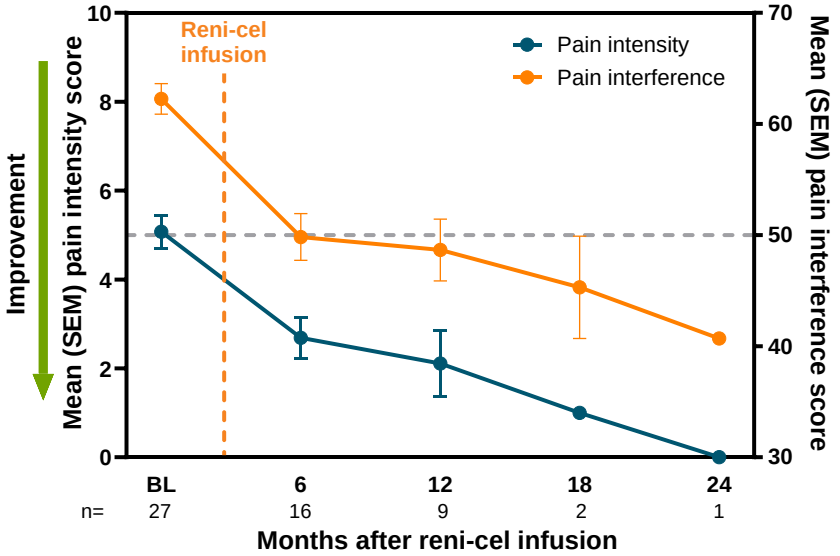
Of 28 treated patients, 27 were VOE-free post-reni-cel infusion as of the data cutoff date



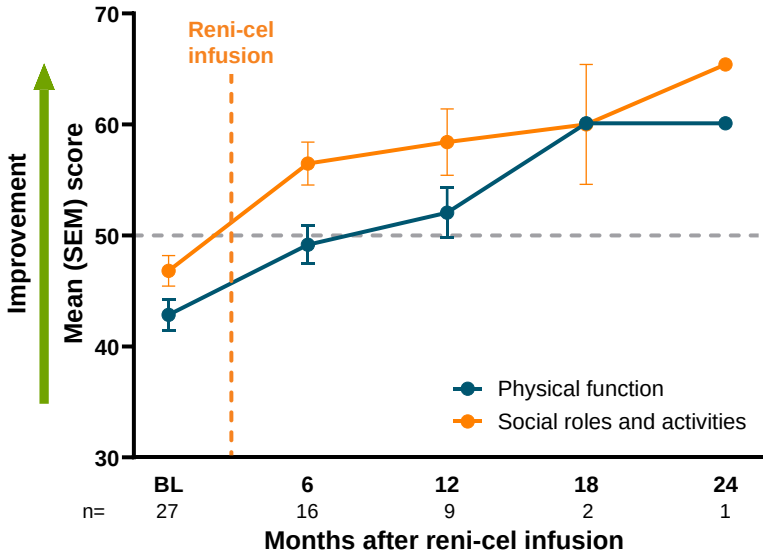
Data cutoff date: October 29th, 2024. Left panel ends at informed consent date: 0* is day of informed consent. Right panel starts at infusion date: 0^ is day reni-cel was infused. †A severe VOE requiring medical attention (despite hydroxyurea or other supportive care measures in the pre-treatment period) is defined as: an acute episode of pain with no cause other than a vaso-occlusion, resulting in either a ≥24 h hospital or ER observation unit or ≥2 visits to a day unit or ER over 72 h with both visits requiring administration of pain medications; acute priapism lasting >2 h and requiring a visit to a medical facility (with or without hospitalization). ‡Non-severe VOE is defined as an acute episode of pain with no medically determined cause other than a vaso-occlusion. §Patient 17 experienced two investigator-reported severe VOEs. The increases in the percentage of HbF and the normal level of total Hb hemoglobin in this patient after reni-cel infusion (44.7% HbF and 14.2 g/dL total Hb at Month 6) were in line with those observed for other treated patients. All study investigator–reported VOEs (pre-consent and post-reni-cel infusion) are under review by a blinded adjudication committee. One post-treatment severe VOE was adjudicated as not being a VOE. The second post-treatment severe VOE is pending review.
ER, emergency room; h, hour; Hb, hemoglobin; HbF, fetal hemoglobin; reni-cel, renizgamglogene autogedtemcel; VOE, vaso-occlusive event.

PROs: Mean scores for pain intensity, pain interference, physical function, and social roles and activities were improved after reni-cel infusion

A. Pain domains



B. Physical and social domains



Data cutoff date: October 29th, 2024. Data were collected using PROMIS-57. Dotted gray line indicates normative value for relevant reference population.
BL, baseline; PRO, patient-reported outcome; PROMIS-57, Patient-Reported Outcome Measurement System — Profile 57; reni-cel, renizgamglogene autogedtemcel; SEM, standard error of the mean.

Reni-cel safety profile reflected busulfan myeloablative conditioning and autologous HSCT

TEAE CATEGORY	N=28 Number of patients (%)	N=28 Number of events
Any TEAE	28 (100)	618
Any TEAE related to reni-cel*	3 (10.7)	6
Any TEAE related to busulfan	27 (96.4)	322
Any serious TEAE	12 (42.9)	26
Any serious TEAE related to reni-cel†	2 (7.1)	2
Any Grade 3 or 4 TEAE	27 (96.4)	144
Any Grade 3 or 4 TEAE related to reni-cel†	2 (7.1)	2
Any TEAE related to reni-cel leading to discontinuation	0 (0)	0
Any TEAE leading to death	0 (0)	0

Data cutoff date: October 29th, 2024. *TEAEs related to reni-cel included gastroenteritis eosinophilic, increased hematocrit, increased hemoglobin, infusion related reaction, and acute respiratory distress syndrome. †Two patients in the RUBY study experienced serious TEAEs of Grade ≥3 assessed by the investigator as possibly related to reni-cel. One patient experienced Grade 4 acute respiratory distress syndrome with onset at 11 days post-reni-cel infusion and assessed as resolved by 21 days post-reni-cel infusion. The TEAE was assessed as possibly related to reni-cel and busulfan and related to the transplant procedure. Potentially contributing factors include the patient's history of recurrent ACS, mild obstructive pattern observed in pulmonary function test, recent history of smoking/vaping, and G-CSF administration. The patient has remained clinically stable since discharge from hospital. The other patient experienced Grade 3 gastroenteritis eosinophilic with onset at 47 days post-reni-cel infusion, which was ongoing as of the data cutoff date. The TEAE was assessed as possibly related to reni-cel, given the unclear etiology, with investigative work-up continuing. The patient has an ongoing medical history of eczema with no documented food allergies.

ACS, acute chest syndrome; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell treatment; reni-cel, renizgamglogene autogedtemcel; TEAE, treatment-emergent adverse event.

Conclusions

- Patients achieved early correction of anemia / normal Hb, and sustained HbF induction to ≥40% total Hb with pancellular distribution
- Markers of hemolysis improved or normalized by Month 6
- 27 of 28 treated patients were VOE-free post-reni-cel infusion as of the data cutoff date
- Early and sustained meaningful improvements were observed in pain, physical, and social patient-reported outcome domains

- The safety profile was consistent with myeloablative conditioning with busulfan and autologous HSCT

- Reni-cel treatment showed promising results, with clinically meaningful improvements after gene editing at the *HBG1/2* promoters with AsCas12a

Data cutoff date: October 29th, 2024.

AsCas12a, *Acidaminococcus* sp. Cas12a; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; Hb, hemoglobin; HbF, fetal hemoglobin; *HBG1/2*, γ-globin genes 1 and 2; HSCT, hematopoietic stem cell treatment; reni-cel, renizgamglogene autogedtemcel; VOE, vaso-occlusive event.

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Data first presented at ASH Annual Meeting and Exposition, San Diego, CA, December 7–10, 2024.

Supplemental Information

Supplement Table 1. Markers of hemolysis

Mean levels of markers of hemolysis, ARC, indirect bilirubin, and lactate dehydrogenase normalized by Month 6 post-reni-cel infusion and were generally maintained or further improved by Month 12

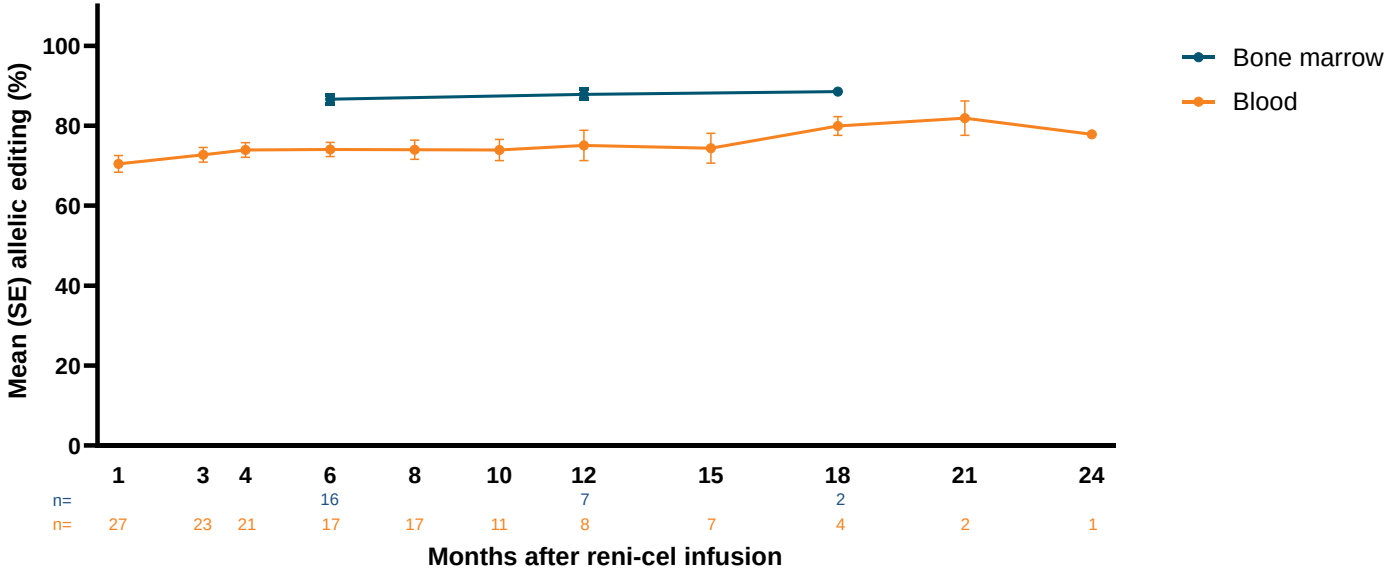
Visit	Absolute reticulocyte count (× 10^6 cells/μL)	Indirect bilirubin (μmol/L)	Lactate dehydrogenase (U/L)	Haptoglobin (g/L)
Baseline				
Mean	0.211	45.2	401.1	0.101
(SD)	(0.102)	(27.2)	(197.3)	(0.159)
n	n=21*	n=26	n=26	n=26
Month 6				
Mean	0.081	12.2	174.9	0.482
(SD)	(0.021)	(7.0)	(41.3)	(0.319)
n	n=17	n=17	n=15	n=16
Month 12				
Mean	0.091	10.2	159.9	0.511
(SD)	(0.027)	(4.1)	(10.9)	(0.448)
n	n=9	n=9	n=8	n=9
Month 18				
Mean	0.087	7.6	171.7	0.446
(SD)	(0.021)	(0.8)	(27.1)	(0.670)
n	n=3	n=3	n=3	n=3
Reference range	Females: 0.01–0.12 Males: 0.01–0.14	0.0–16.6	113–226	0.3–2.0

Data cutoff date: October 29th, 2024. Analysis excludes two patients due to adverse event or medical history of Gilbert's syndrome or G6PD deficiency. *Baseline ARC was not obtained for five patients because this assessment was included in a protocol amendment after these subjects had completed their baseline visit.

ARC, absolute reticulocyte count; reni-cel, renizgamglogene autogedtemcel; SD, standard deviation.

Supplement Figure 1. Allelic editing levels

Patients showed sustained high levels of allelic editing in both peripheral blood nucleated cells and bone marrow–derived CD34^{+} cells, with mean (SD) editing levels of 75.1% (10.8% [n=8]) and 87.8% (3.35% [n=7]) at Month 12, respectively



Data cutoff date: October 29th, 2024.
CD, cluster of differentiation; reni-cel, renizgamglogene autogedtemcel; SD, standard deviation; SE, standard error.