Reni-cel, the first AsCas12a gene-edited cell therapy, led to hemoglobin normalization and increased fetal hemoglobin in severe sickle cell disease patients in an interim analysis of the RUBY trial

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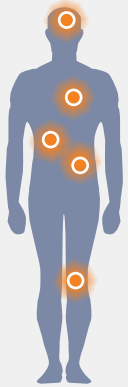
Sickle Cell Disease Is a Life-Threatening Hematological Disorder

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



Lifelong complications, multi-organ damage, and comorbidities **reduce quality of life** and **shorten lifespan**[1–4]

There remains a continued **unmet need** for treatment options with curative intent for patients with **SCD** who lack an HLA-matched related donor[4]

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

Hemoglobin

Sustained hemoglobin at the normal physiological range **reduces** risk for **end-organ damage** and other **negative clinical outcomes** in patients with SCD[5]

Fetal hemoglobin

Sustained increases in fetal hemoglobin levels correlate with **reduction** or **elimination** of SCD **symptoms,** including VOEs[6–9]

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

1. Royal CDM *et al. Adv Genet* 2021; 2(1): e10037. 2. Modell B and Darlison, M. *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. Ershler WB *et al. Curr Ther Res Clin Exp* 2023; 98: 100696. 6. Powars DR *et al. Blood* 1984; 63 (4): 921–926. 7. Charache S *et al. N Engl J Med* 1995; 332 (20): 1317–1322. 8. Frangoul H *et al. NEJM* 2024; 390 (18): 1649–1662. 9. 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 and Correct Anemia

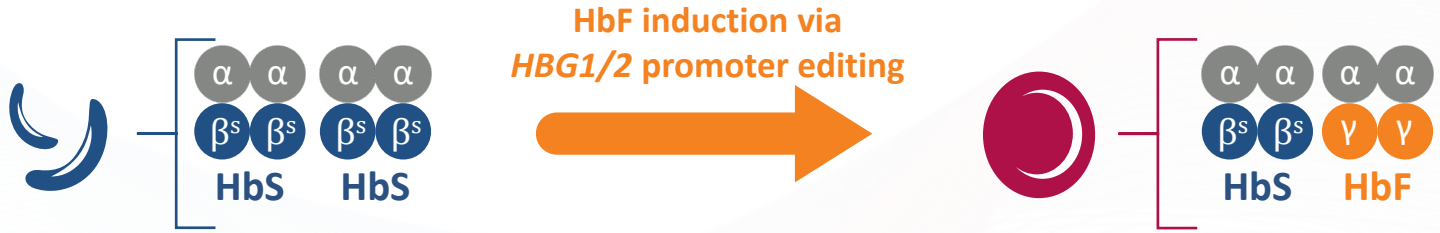
Renizgamglogene autogedtemcel (reni-cel) is an investigational gene-edited autologous hematopoietic stem cell medicine

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

Targeting ***HBG1 and HBG2*** promoter regions to mimic naturally occurring mechanisms of HPFH[2]

With edits in the *HBG1* and *HBG2* promoter regions, reni-cel mimics naturally occurring variants of HPFH to reactivate γ-globin expression and increase HbF production

Reni-cel Mechanism of Action in SCD



α, α-globin; β, β-globin; β^S, sickle β-globin; γ, γ-globin; AsCas12a, *Acidaminococcus sp.* clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 12a; *HBB*, β-globin gene; HbF, fetal hemoglobin; *HBG*, γ-globin gene; HbS, sickle hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; RBC, red blood cell; 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.

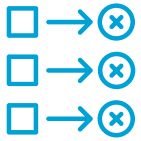
The RUBY Trial is Evaluating the Safety, Tolerability, and Efficacy of Reni-cel in Patients With Severe SCD

Design

- Phase 1/2/3
- International, multicenter
- Open-label, single-arm study
- 24 months of follow-up post-reni-cel infusion

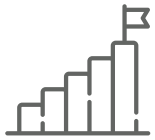
Key Inclusion Criteria

- 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 Emergency Room (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); acute chest syndrome (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; HLA, human leukocyte antigen; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; VOE, vaso-occlusive event.

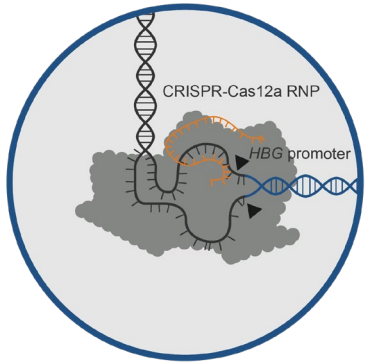
ClinicalTrials.gov NCT04853576. Available at: https://clinicaltrials.gov/ct2/show/NCT04853576. Accessed May 2024.

Patients in the RUBY Trial Receive a Single Infusion of Reni-cel and are Monitored for 24 Months

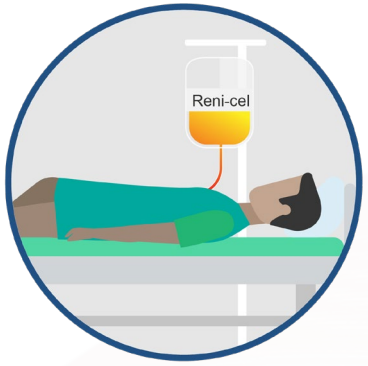
SCREENING → **MOBILIZATION & APHERESIS** → **DRUG PRODUCT MANUFACTURING** → **MYELOABLATION & RENI-CEL INFUSION** → **ENGRAFTMENT & 24 MONTH FOLLOW-UP**

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 CRISPR-associated protein 12a; 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.

All Treated Patients Showed Successful Engraftment

DEMOGRAPHICS	(N=18)
Genotype, n (%)	
β^S/β^S	17 (94.4)
β^S/β^0	1 (5.6)
Sex, n (%)	
Female	9 (50.0)
Age, years, median (min, max)	27.0 (18.0, 35.0)
Severe VOEs, pre-study annual rate*, mean (SD)	5.2 (2.9)

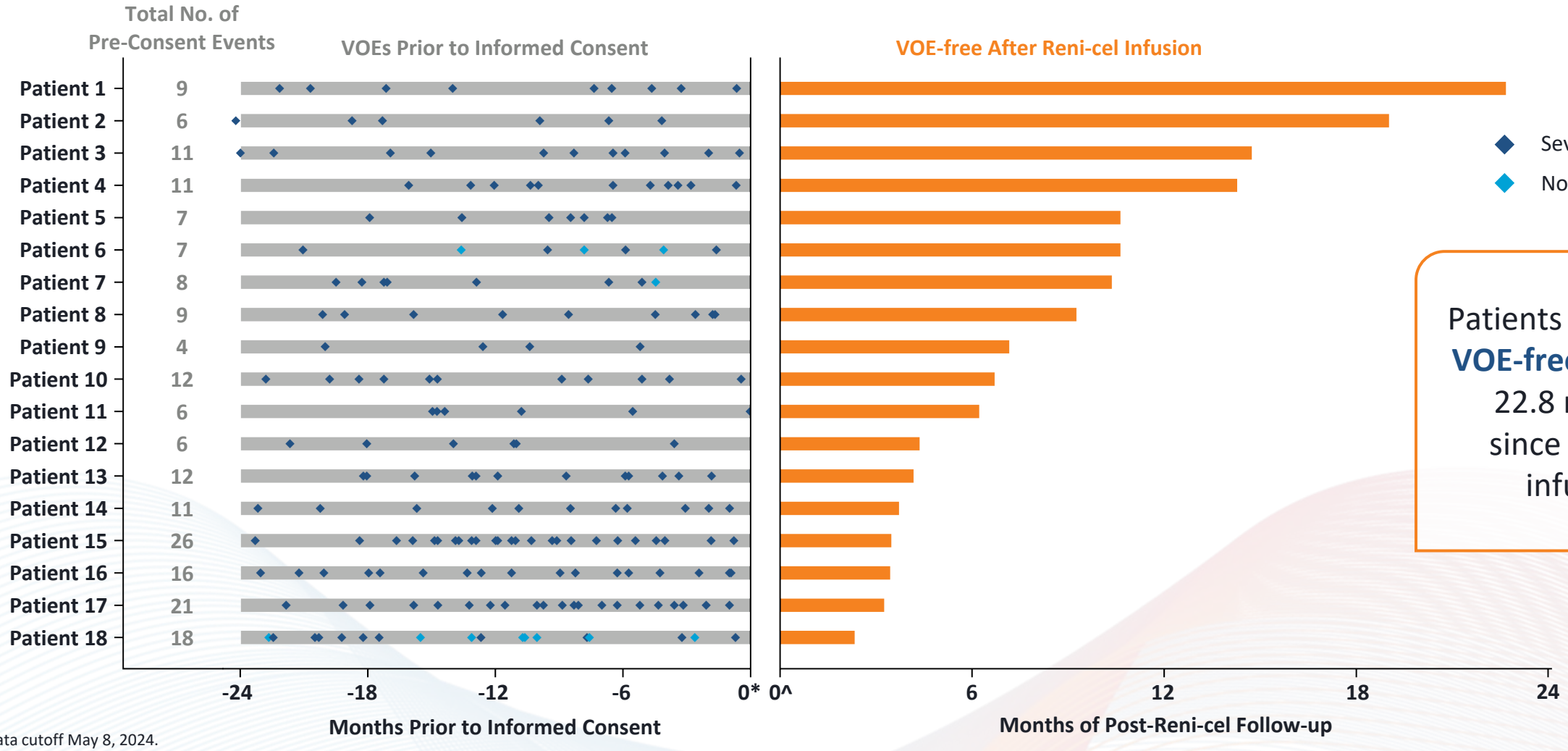
APHERESIS, INFUSION, AND ENGRAFTMENT	(N=18)
Number of mobilization and apheresis cycles†, median (min, max)	2.0 (1.0, 4.0)
Total reni-cel dose administered, × 10^6 $CD34^+$ cells/kg, median (min, max)	4.6 (2.9, 10.0)
Follow-up duration, months, median (min, max)	7.0 (2.4, 22.8)
Time to neutrophil engraftment‡, days, median (min, max)	23.0 (15.0, 29.0)
Time to platelet engraftment§, days, median (min, max)	24.0 (18.0, 51.0)

Data cutoff May 8, 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 and back-up rescue cells. Some patients underwent a cycle of leukapheresis solely for collection of rescue cells. ‡Three consecutive measurements with absolute neutrophil count (ANC) ≥0.5 × 10^9/L. §Three consecutive measurements with platelet count ≥50 × 10^9/L starting at least 7 days after the platelet transfusion, and 10 days after thrombopoietin (TPO). No TPO was used for patients after reni-cel infusion.

β, β-globin allele; *HBG*, γ-globin gene; max, maximum; min, minimum; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; SD, standard deviation; VOE, vaso-occlusive event.

All Patients Treated with Reni-cel are VOE-free



Patients have been **VOE-free** for up to 22.8 months since reni-cel infusion

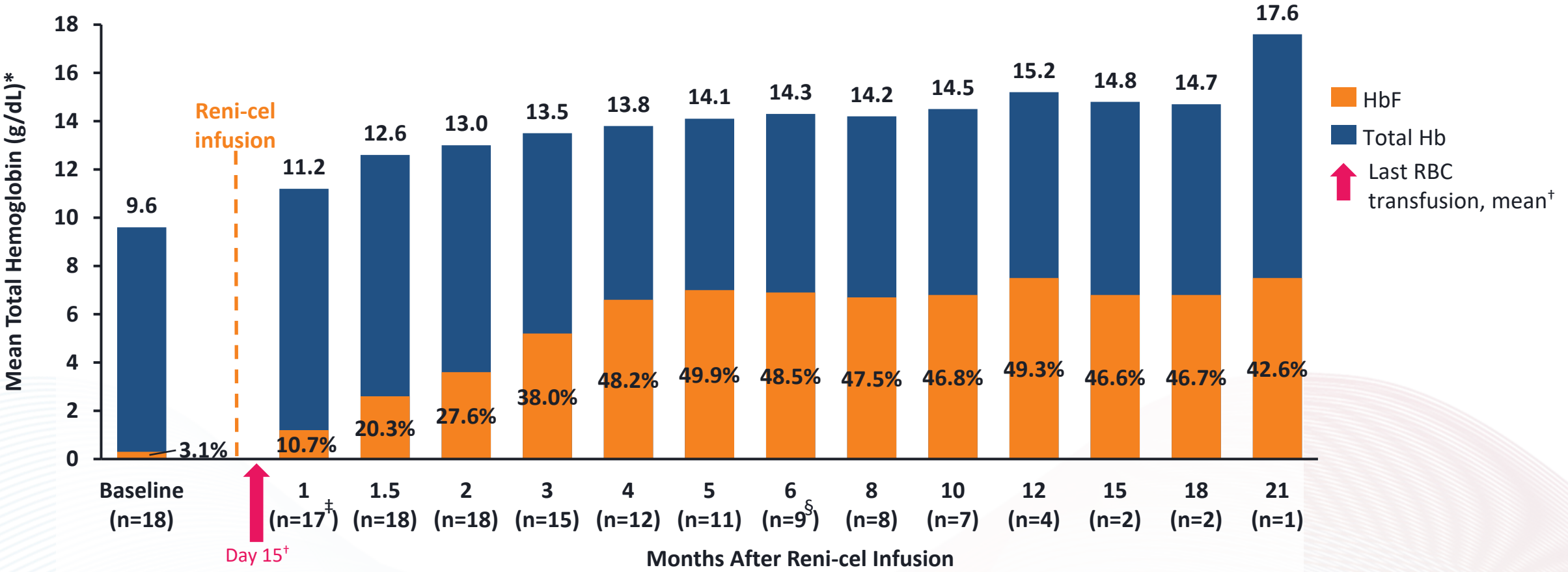
Data cutoff May 8, 2024.

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 Emergency Room (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); acute chest syndrome (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. ‡Non-Severe VOE is defined as an acute episode of pain with no medically determined cause other than a vaso-occlusion.

reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; VOE, vaso-occlusive event.

Patients had Rapid and Sustained Clinically Meaningful Improvements in HbF (>40%), with Early and Durable Normalization of Hb



Markers of hemolysis (reticulocyte count, indirect bilirubin, LDH, and haptoglobin) displayed a trend of **improvement** or have **normalized** in treated patients

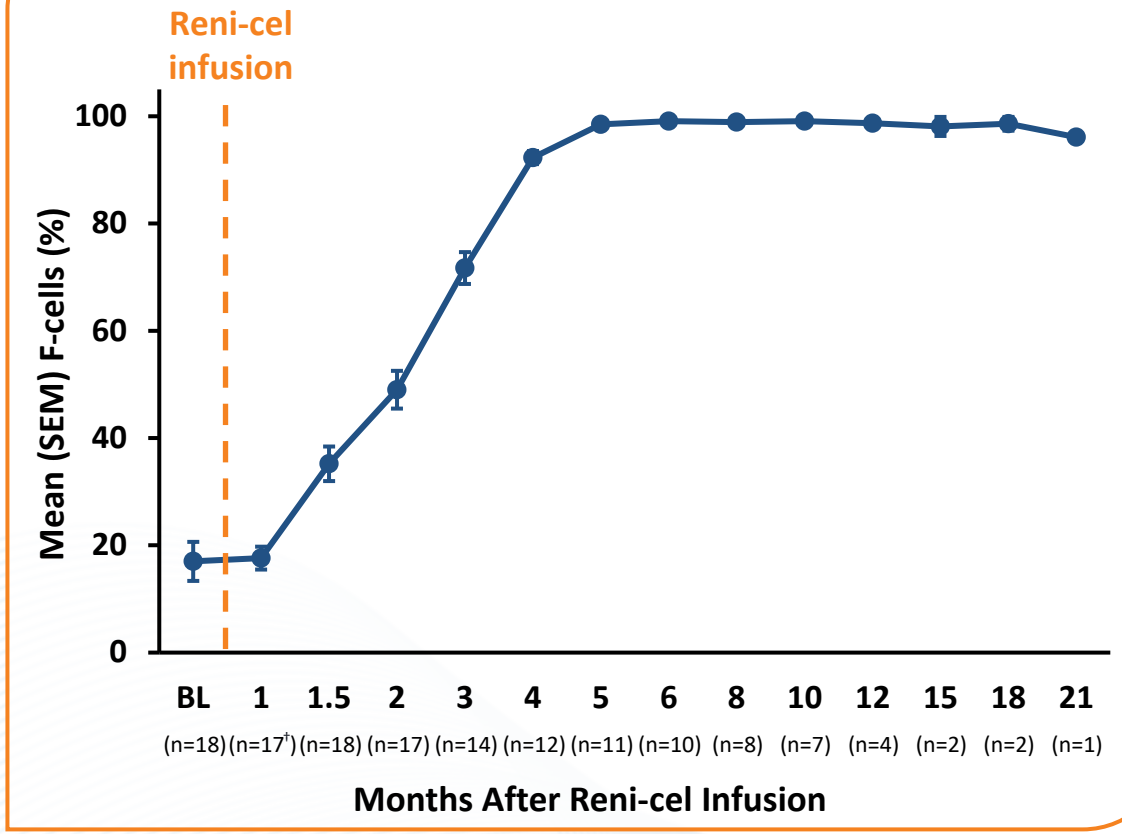
Data cutoff May 8, 2024. Number of male patients = 9; number of female patients = 9. Bars show mean Hb (g/dL). Labels inside / next to the bars indicate mean proportion of HbF as a percentage of total Hb. Mean total Hb concentrations are shown directly above bars.

*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 in patients occurred a mean (SD) of 14.6 (5.6) days after reni-cel infusion (n=18). ‡One patient did not have central labs performed at Month 1 because of venous access issues. §n=10 for HbF percentage; total Hb and absolute HbF were not provided by the central lab at Month 6 for one patient because the sample was clotted.

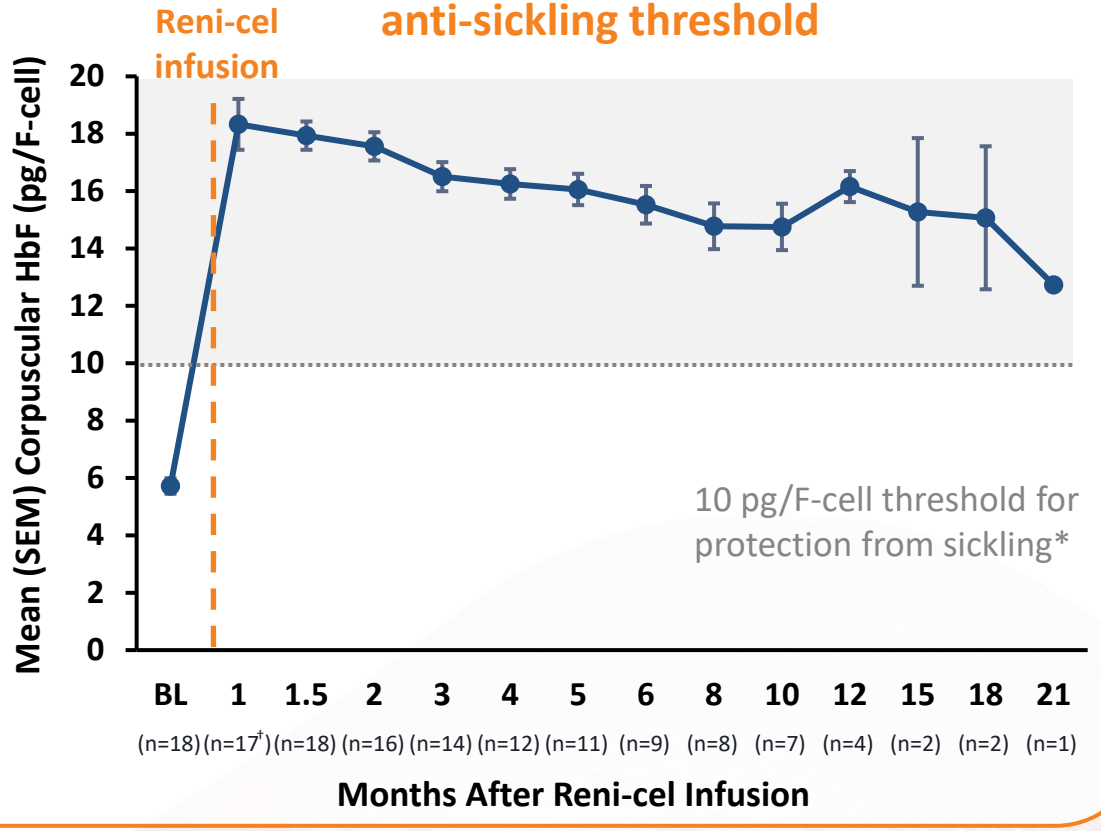
Hb, hemoglobin; HbF, fetal hemoglobin; LDH, lactate dehydrogenase; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel.

Patients Showed Pancellular Distribution of HbF in RBCs, with Sustained Levels Above the Anti-Sickling Threshold

Percentage of F-cells increased early



MCH-F/F-cell was sustained above the anti-sickling threshold



Patients showed **sustained high levels of editing** in the *HBG1* and *HBG2* promoter regions:

At Month 6, mean (SD) editing levels were 75.7% (8.6%) in patient **peripheral blood nucleated cells** (n=8) and 87.6% (3.2%) in patient **bone marrow–derived CD34⁺ cells** (n=10), with high editing levels maintained at last follow-up

Data cutoff May 8, 2024.

*Based on data from Steinberg MH *et al*, *Blood* 2014; 123 (4): 481–485. †One patient did not have central labs performed at Month 1 because of venous access issues.

BL, baseline; HbF, fetal hemoglobin; *HBG*, γ-globin gene; MCH-F/F-cell, mean HbF concentration/F-cell; RBC, red blood cell; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; SD, standard deviation; SEM, standard error of the mean.

Safety Profile of Reni-cel Is Consistent With That of Myeloablative Conditioning With Busulfan and HSCT

TEAE CATEGORY	N=18 Number of patients (%)	Number of events
Any TEAE	18 (100)	374
Any TEAE related to reni-cel*	1 (5.6)	1
Any TEAE related to busulfan	18 (100)	206
Any serious TEAE†	7 (38.9)	9
Any serious TEAE related to reni-cel	0 (0)	0
Any Grade 3 or 4 TEAE	17 (94.4)	82
Any Grade 3 or 4 TEAE related to reni-cel	0 (0)	0
Any TEAE related to reni-cel leading to discontinuation	0 (0)	0
Any TEAE leading to death	0 (0)	0

No serious TEAEs were reported as related to reni-cel

Data cutoff May 8, 2024.

*One patient experienced a non-serious TEAE of Grade 1 Alanine aminotransferase increased (1.2 × ULN), which was reported to be causally related to reni-cel and busulfan. The TEAE has resolved, and alanine aminotransferase level normalized.

†As of the data cut, serious TEAEs in the RUBY trial included gastroenteritis, gastroenteritis viral, pneumonia, sepsis, chills, and hyperglycemia.

HSCT, hematopoietic stem cell transplantation; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; TEAE, treatment emergent adverse event; ULN, upper limit of normal.

Conclusions

Reni-cel is an investigational autologous gene-edited medicine that demonstrates promising results for gene editing of the **γ-globin gene (*HBG1* and *HBG2*) promoters** to induce HbF expression in patients with SCD and is the **first clinical use of AsCas12a**

Robust and clinically **meaningful improvements** were observed after treatment with reni-cel*

- All patients are **VOE-free** post-reni-cel infusion
- Patients experienced early **correction of anemia**, with durable **normalization of total Hb**
- **Increases in HbF** and the **percentage of F-cells** were sustained at >40% and >90%, respectively
- Patients also showed a trend in **improvement** or **normalization** of **markers of hemolysis**
- Data from treated patients demonstrated early engraftment and a **safety profile consistent** with myeloablative busulfan conditioning and autologous HSCT

Treatment with reni-cel showed a favorable safety profile and promising preliminary efficacy, supporting further investigation as a differentiated gene-edited medicine for patients with SCD

*Reflects data based on a data cutoff of May 8, 2024.

AsCas12a, *Acidaminococcus sp.* clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 12a; Hb, hemoglobin; HbF, fetal hemoglobin; reni-cel, renizgamglogene autogedtemcel; SCD, sickle cell disease; VOE, vaso-occlusive event.

Acknowledgements

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