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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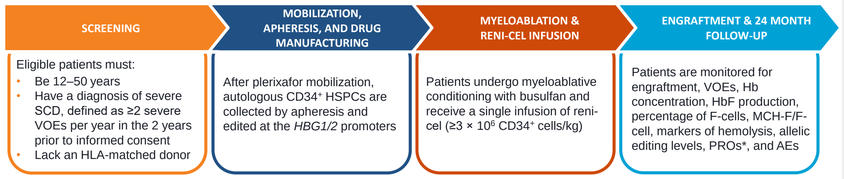
INTRODUCTION

- Sustained increases in fetal hemoglobin (HbF, α2γ2) can reduce or eliminate sickle cell disease (SCD) symptoms, including vaso-occlusive events (VOEs)[1]
- Renizgamglogene autogedtemcel (reni-cel) is an investigational gene-edited autologous hematopoietic stem cell medicine comprised of CD34⁺ cells edited at the distal CCAAT box (-118 to -113) of the promoter regions of the γ-globin genes (*HBG1/2*) with a highly specific and efficient, engineered gene-editing nuclease, AsCas12a[2]
- These edits mimic naturally occurring variants of hereditary persistence of HbF in the *HBG1/2* promoters and reactivate γ-globin expression, resulting in sustained and clinically meaningful production of HbF[3]
- The ongoing RUBY trial (NCT04853576) is a Phase I/II/III, multicenter, open-label, single-arm study evaluating safety, tolerability, and efficacy of reni-cel in patients with severe SCD

METHODS

Figure 1: RUBY study design



*PROs were evaluated using PROMIS-57 at regular intervals throughout the study.
AEs, adverse events; CD, cluster of differentiation; Hb, total hemoglobin; HbF, fetal hemoglobin; *HBG1/2*, γ-globin genes; HLA, human leukocyte antigen; HSPC, hematopoietic stem and progenitor cells; MCH-F, mean corpuscular fetal hemoglobin; PROs, patient-reported outcomes; PROMIS-57, Patient-Reported Outcome Measurement System — Profile 57; SCD, sickle cell disease; VOE, vaso-occlusive event.

- Data presented are based on a cutoff date of Oct 29, 2024

RESULTS: BASELINE CHARACTERISTICS

- Patients treated in the study (N=28) are broadly representative of the overall population of patients with severe SCD
- Patients had severe disease burden, experiencing a mean of 4.6 severe VOEs annually and substantial pain at baseline (baseline Pain Numerical Rating Scale [NRS] = ~5.1)
- Patients were a median (range) of 9.5 (0.7–25.2) months post-reni-cel infusion, with 11 patients having >1 year follow-up
- All treated patients showed successful engraftment and promising engraftment kinetics, which is important for limiting infection and bleeding risk

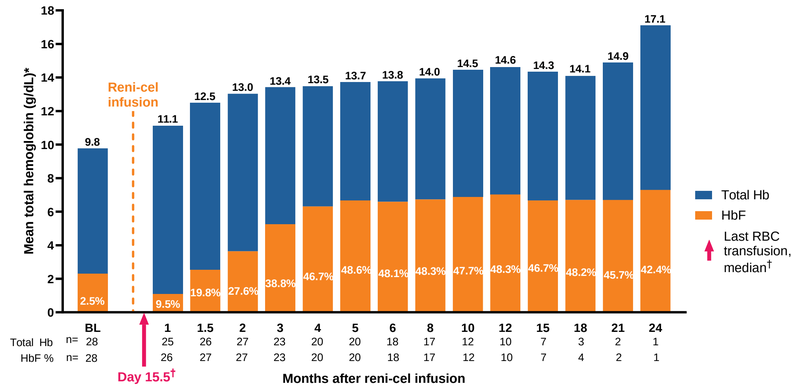
Table 1. RUBY patient demographics, baseline characteristics, and treatment characteristics

Parameter	Reni-cel (N=28)
Demographics and baseline characteristics	
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 and apheresis, infusion, and engraftment	
Number of mobilization and apheresis cycles† (median, range)	2.0 (1.0–4.0)
Total reni-cel dose administered, ×10⁶ 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)

SCD, sickle cell disease; SD, standard deviation; VOE, vaso-occlusive event.
*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 absolute neutrophil count (ANC) ≥0.5 × 109/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 × 109/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. Based on 27 patients who had achieved platelet engraftment by the time of the data cut.

RESULTS: EFFICACY

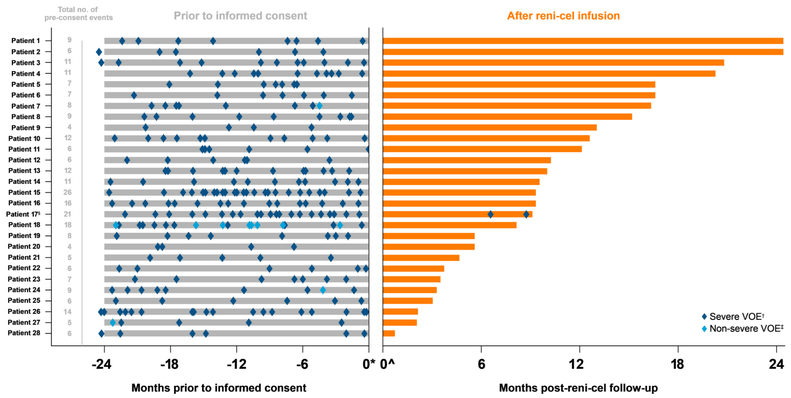
Figure 2: After reni-cel infusion, patients achieved early correction of anemia, with durable normalization of Hb and sustained increases in HbF



Total number of female patients = 15; no. 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; RBC, red blood cell; Hb, hemoglobin; HbF, fetal hemoglobin.

- The percentage of F-cells (**Supp Figure 1**) and mean corpuscular fetal hemoglobin (MCH-F)/F-cell (**Supp Figure 2**) increased early, and MCH-F/F-cell was sustained above the anti-sickling threshold of 10 pg/F-cell through last follow-up
- Markers of hemolysis, including absolute reticulocyte count, indirect bilirubin, lactate dehydrogenase, and haptoglobin, improved or normalized by Month 6 and were generally maintained over time (**Supp Table 1**)
- 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 (**Supp Figure 3**)

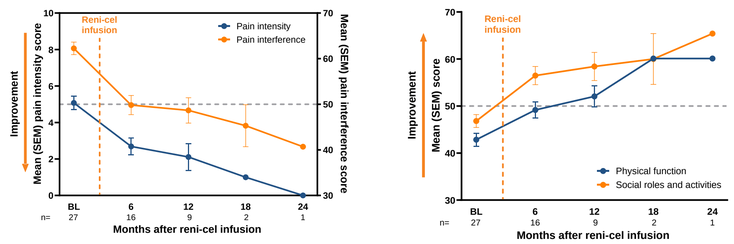
Figure 3: Of 28 treated patients, 27 were VOE-free post-reni-cel infusion as of the data cutoff date



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. ‡Severe VOE and ‡non-severe VOE are defined in the supplemental methods, which can be accessed by scanning the QR code in the bottom right corner of the poster. §Patient 17 experienced two investigator-reported severe VOEs. Approximately 6.6 months after reni-cel infusion (Study Day 197), this patient was hospitalized due to dyspnea on exertion, chest pain, and diagnosis of COVID-19 infection. During hospitalization, the patient experienced persistent pain in the hips, lower back, and joints that was assessed by the investigator as a severe VOE. COVID-19 infection and the severe VOE were considered resolved within 10 days following treatment with remdesivir and analgesics. Onset of the second investigator-reported severe VOE occurred approximately 8.7 months after reni-cel infusion (Study Day 262). The patient experienced pain in the back, hip, and abdomen, which resolved within 5 days of hospitalization following treatment with analgesics and intravenous hydration. The patient has a medical history of avascular necrosis of the right hip and chronic pain related to SCD. In the two years prior to consent this patient experienced 21 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.
Hb, hemoglobin; HbF, fetal hemoglobin; RBC, red blood cell; SCD, sickle cell disease; VOE, vaso-occlusive event.

RESULTS: EFFICACY

Figure 4: Improvements in mean scores for pain intensity, pain interference, physical function, and social roles and activities were observed after reni-cel infusion



Data were collected using PROMIS-57. Dotted grey line indicates normative value for relevant reference population.
BL, baseline; PROMIS-57, Patient-Reported Outcome Measurement System — Profile 57; SEM, standard error of the mean.

RESULTS: SAFETY

Table 2. The safety profile of reni-cel was consistent with myeloablative conditioning with busulfan and autologous hematopoietic stem cell treatment (HSCT)

	Reni-cel (N=28)	
TEAE category	No. of patients (%)	No. 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
Any TEAE leading to death	0	0

*TEAEs related to reni-cel included Gastroenteritis eosinophilic, Hematocrit increased, Hemoglobin increased, 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; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Reni-cel treatment showed promising results, with robust and clinically meaningful improvements, for gene editing at the *HBG1/2* promoters with AsCas12a
- Patients achieved early correction of anemia, durable normalization of total hemoglobin, and sustained increase in HbF ≥40% 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 busulfan conditioning and autologous HSCT

REFERENCES

1. Steinberg MH. *Blood* 2020; 136 (21): 2392–2400. 2. Hanna R *et al. HemaSphere* 2024; 8: (S1): 404–405. 3. Canver MC *et al. Blood* 2016; 127 (21): 2536–2545.

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Supplement Methods

VOE definitions

†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.

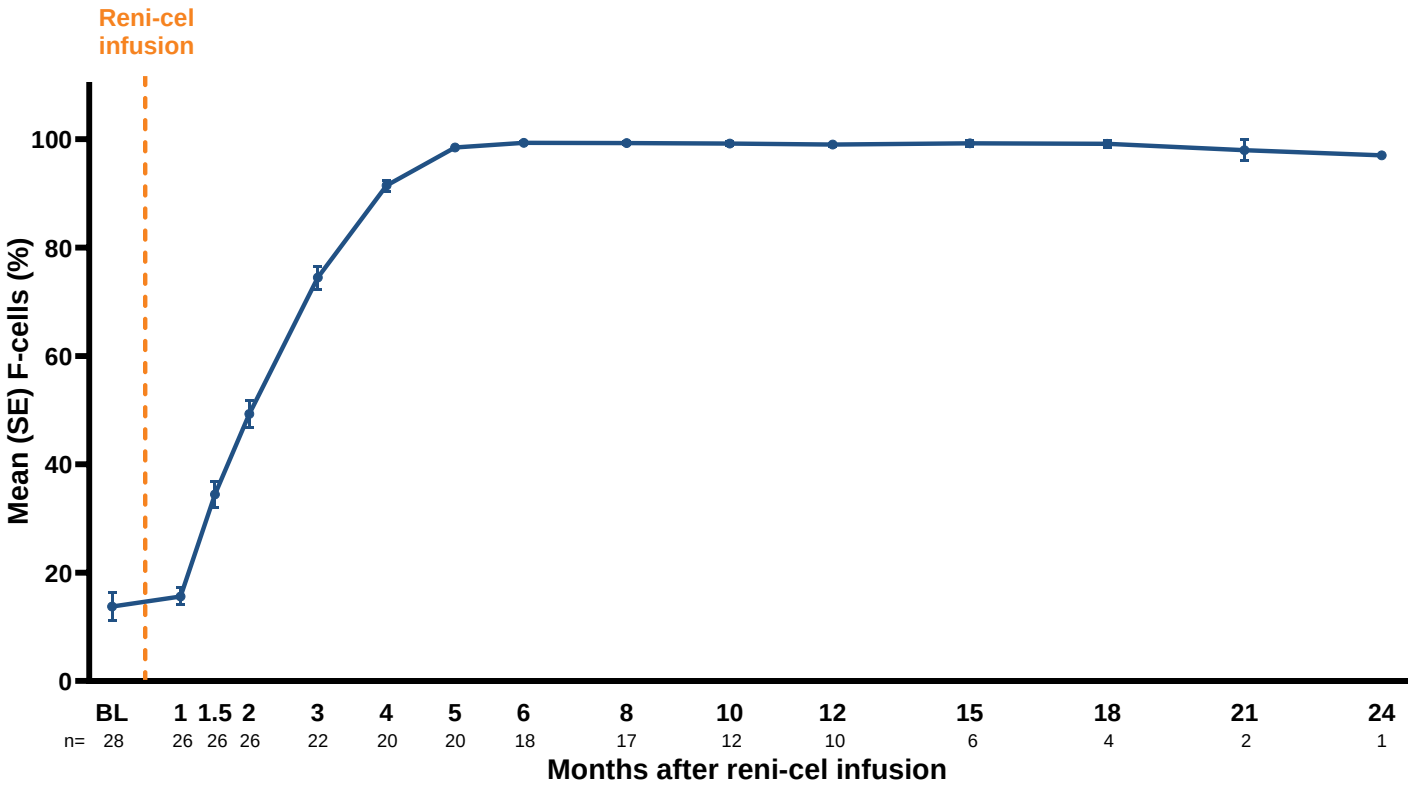
‡Non-severe VOE is defined as an acute episode of pain with no medically determined cause other than a vaso-occlusion.

ACS, acute chest syndrome; ER, Emergency Room; h, hour; VOE, vaso-occlusive event.

Supplement Figures and Table

By Month 6 (n=18), the mean (SD) percentage of F-cells had increased to 99.3% (0.9%) and levels were maintained at >97% through last follow-up (**Supp Figure 1**)

Supplemental Figure 1. Percentage of F-cells

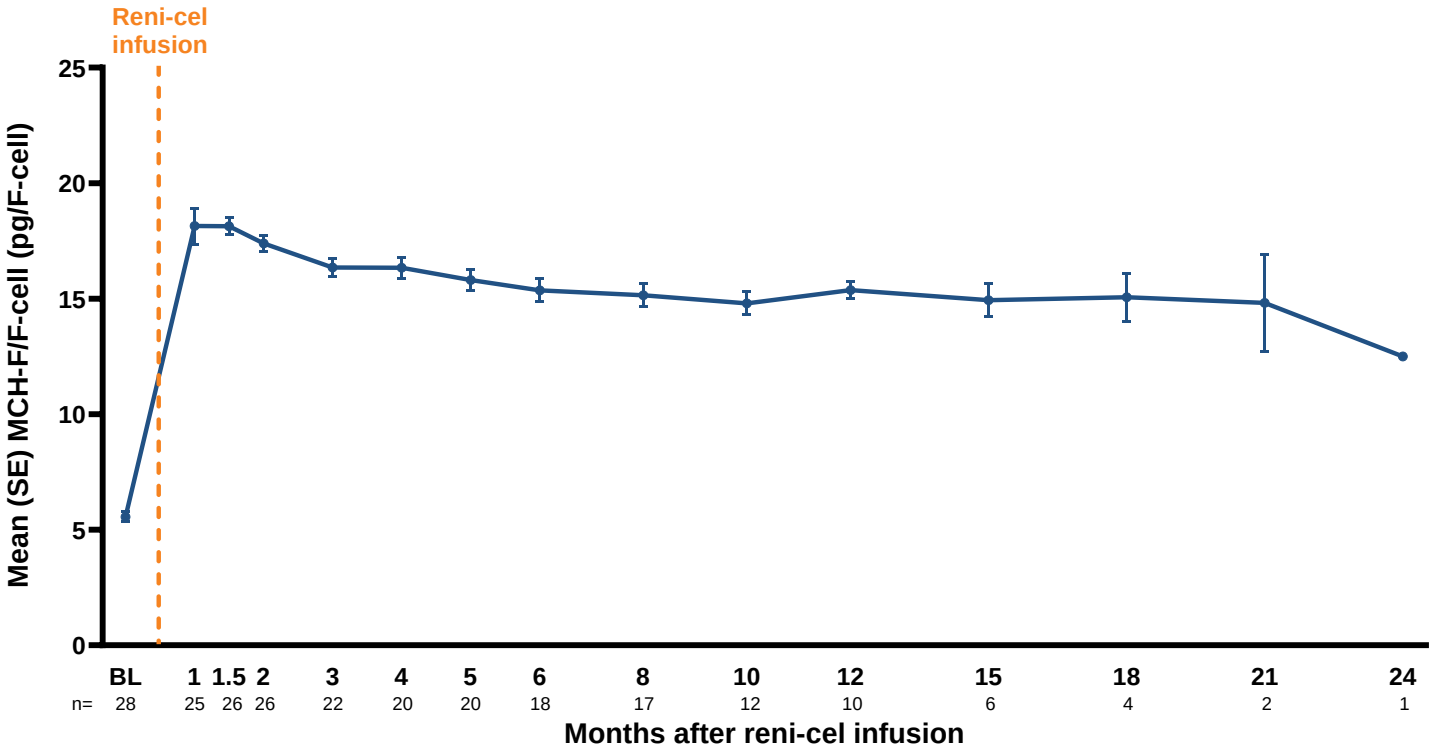


BL, baseline; F-cells, red blood cells expressing fetal hemoglobin; SD, standard deviation; SE, standard error

Supplement Figures and Table

Mean corpuscular HbF per F-cell (MCH-F/F-cell) increased early and was maintained above 10 pg/F-cell (**Supp Figure 2**)

Supplemental Figure 2. MCH-F/F-cell



BL, baseline; MCH-F, mean corpuscular fetal hemoglobin; SE, standard error.

Supplement Figures and Table

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 (**Supp Table 1**)

Supplemental Table 1. Markers of hemolysis

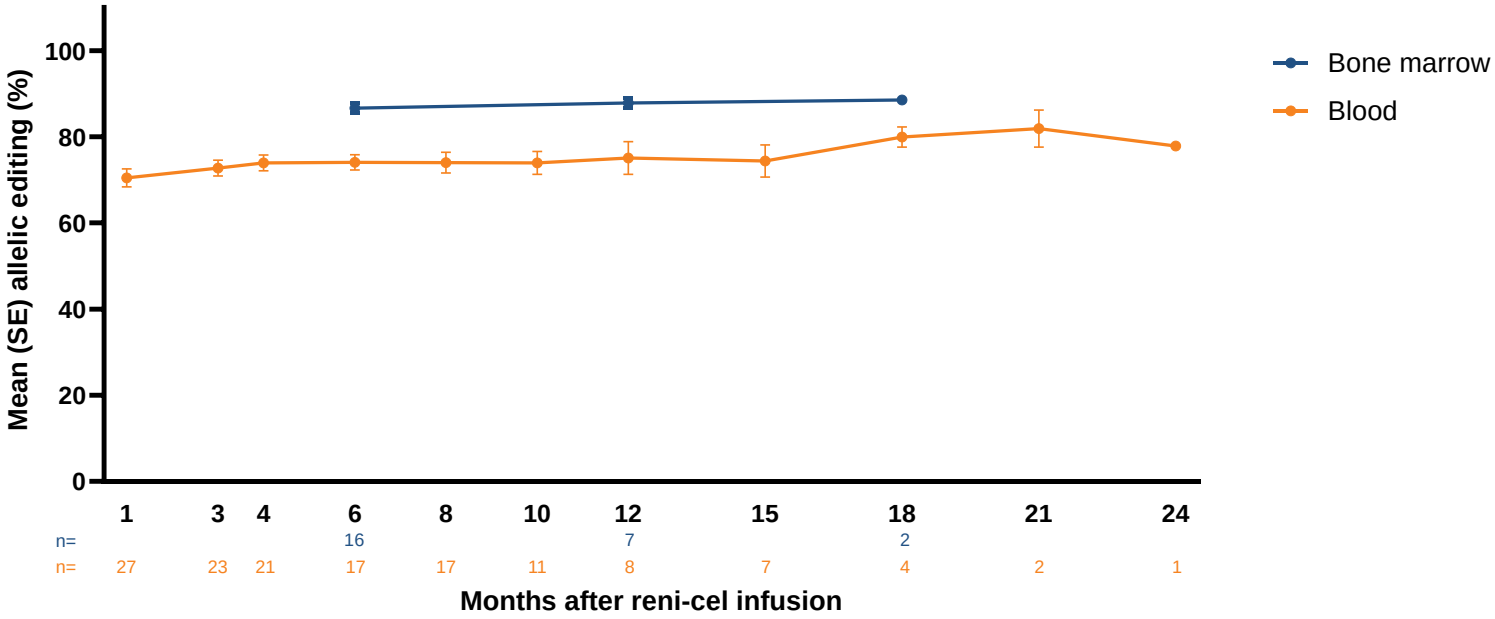
Visit	Absolute reticulocyte count (× 10^6 cells/μL)	Indirect bilirubin (μmol/L)	Lactate dehydrogenase (U/L)	Haptoglobin (g/L)
Baseline				
Mean	0.211	45.2	401.1	0.101
(SD)	(0.102)	(27.2)	(197.3)	(0.159)
n	n=21*	n=26	n=26	n=26
Month 6				
Mean	0.081	12.2	174.9	0.482
(SD)	(0.021)	(7.0)	(41.3)	(0.319)
n	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

ARC, absolute reticulocyte count; SD, standard deviation.
Analysis excludes two patients due to adverse event or medical history of Gilbert's syndrome or G6PD deficiency. *Baseline absolute reticulocyte count was not obtained for 5 patients because this assessment was included in a protocol amendment after these subjects had completed their baseline visit.

Supplement Figures and Table

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 (**Supp Table 3**)

Supplemental Figure 3. Allelic editing levels



SE, standard error.