Updated Safety and Efficacy Results of RM-001, Autologous HBG1/2 Promoter-modified CD34+ Hematopoietic Stem and Progenitor Cells, in Treating Transfusion-Dependent β-Thalassemia

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INTRODUCTION

- Re-activation of γ-globin expression to increase HbF level is a promising treatment for β-hemoglobinopathies.
- Natural mutations in the γ- globin gene (*HBG1/2*) promoters disrupt the binding of the transcriptional repressors BCL11A could lead to a lifelong persistence of fetal γ-globin expression[1].
- Using gene editing to mimic these mutations should reactivate γ-globin in patients with transfusion-dependent β-thalassemia (TDT) and ameliorate the symptoms of patients.
- RM-001 is a novel cell therapy that uses non-viral, ex vivo CRISPR-Cas9 gene editing in autologous hematopoietic stem and progenitor cells (HSPCs) at the promoter of the γ-globin genes (HBG1/2) to disrupt the binding site of BCL11A[2, 3].

AIM

- Both IIT (ChiCTR2100053406 and ChiCTR2100052858, n =7) and phase I trial (ChiCTR2300069244, n =12) have been conducted to evaluate the safety and efficacy of RM-001 in treating TDT. (data cutoff: Oct 30, 2024)

METHOD

- Patients (6–35 years of age) with TDT and a history of ≥100 mL/kg/year or ≥10 units/year packed red blood cell (pRBC) transfusions in the 2 years before screening were eligible.
- Primary efficacy endpoint: TI12, transfusion-independence for ≥12 consecutive months, maintaining a weighted average hemoglobin (Hb) ≥9 g/dL without pRBC transfusion.
- Key secondary endpoint: TI6, transfusion-independence for ≥6 consecutive months.
- Evaluation of TI12 and TI6 started 60 days after last pRBC transfusion.
- Patients completed the 24-month trial have been enrolled in a long-term follow-up study.

RESULTS

Table 1. Patients and Treatment Characteristics

Patients Characteristics		N = 19
Gender	Male	8
	Female	11
Age, years, mean (range)		14.9 (7.9, 25.6)
6-11 years, n (%)		7 (36.8)
12-17 years, n (%)		5 (26.3)
18-35 years, n (%)		7 (38.8)
Genotype, n (%)	$\beta^0\beta^0$	13(68.4)
	$\beta^0\beta^+$	5 (26.3)
	$\beta^+\beta^+$	1(5.3)
Pre Study pRBC transfusions, U/y, mean (range)		61.3(35.3, 106.3)
Treatment Characteristics		**N = 19**
DP dose, CD34+ cells ×10^6/kg, mean (range)		14.6 (7.9, 21.5)
Neutrophil engraftment, Study day, median (range)		15 (12, 19)
Platelet engraftment, Study day, median (range)		23 (10, 54)
Last pBRC transfusion, Study day, median (range)		25 (10, 95)

Table 2. AEs observed during the study

Post-RM-001 AE Overview	N = 19
Patients with any AEs, n,(%)	19(100.0)
- Patients with AEs related to RM-001, n(%)	3(15.8)
- Patients with AEs related to busulfan, n(%)	19(100.0)
Patients with AEs Grade 3/4, n(%)	19(100.0)
Patients with SAEs, n(%)	4(21.1)
- Patients with SAEs related to RM-001, n(%)	0
- Patients with SAEs related to busulfan, n(%)	4(21.1)
Patients with AEs leading to death, n(%)	0

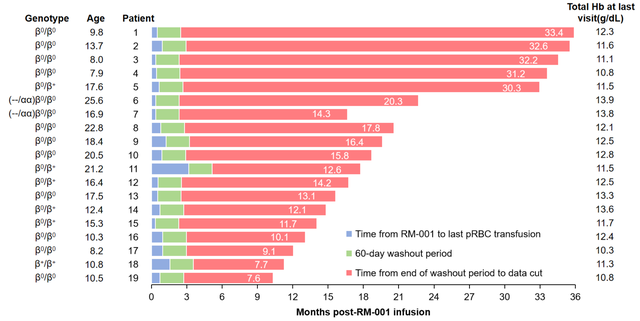
Safety

- The safety profile of RM-001 is generally consistent with myeloablation and autologous hematopoietic stem cell transplantation(HSCT).
- No RM-001-related SAE report. All of AEs have been resolved. No deaths, discontinuations, or malignancies.

Efficacy

- All of 19 (100%) patients stopped transfusions and maintained transfusion-independence ≥ 7 (7.6-33.4) months (Figure 1); The first 5 patients have finished 24-month follow-up and enrolled in a long-term study.
- 13 patients have reached TI12 and the others have reached TI6 (Figure 1).

Figure 1. Patients achieved transfusion independence and had normal Hemoglobin Level



Note: Patients 1-7 from early clinical study and patients 8-19 from phase I trial.

Figure 2. All patients demonstrated substantial increases in HbF level

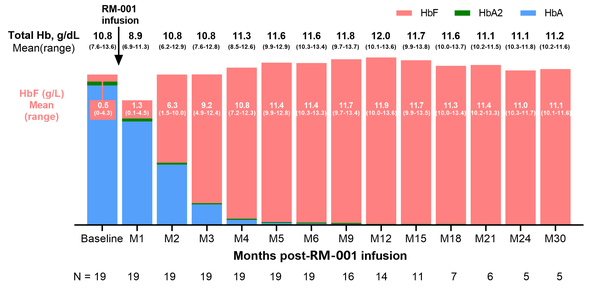
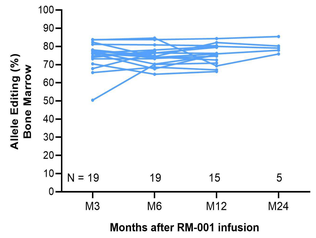


Figure 3. Durable on-target editing in bone marrow cells of patients



- For all patients, the mean HbF were over 10 g/dL at Month 4 and onward (Figure 2).
- Proportion of edited HBG1/2 alleles was stable over time in bone marrow cells (Figure 3).

CONCLUSIONS

- The data from 19 TDT patients infused with RM-001 demonstrated clinically meaningful and sustained increases in total Hb and HbF, leading to transfusion-free in all subjects.
- The safety profile of RM-001 is very well and no product-related serious adverse event was reported during the study.
- After RM-001 infusion, high levels of on-target editing in bone marrow cells were maintained. These results indicate that RM-001 has the potential to cure TDT with one-time treatment.

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