Abstract: P1515

Title: SAFETY AND EFFICACY OF RM-001, AUTOLOGOUS HBG1/2 PROMOTER-MODIFIED CD34+ HEMATOPOIETIC STEM AND PROGENITOR CELLS, IN TRANSFUSION-DEPENDENT Β-THALASSEMIA

Abstract Type: Poster Presentation

Topic: Thalassemias

Background:

Reactivating fetal globin (HbF) is a promising treatment for β-hemoglobinopathies. RM-001 is a novel cell therapy designed to reactivate fetal hemoglobin (HbF) via *ex vivo* CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the BCL11A binding sites on the promoter of the γ-globin genes (*HBG1/2*) in patients (pts) with transfusion-dependent β-thalassemia (TDT).

Aims:

Here, we report the updated safety and efficacy results from ongoing trials of RM-001 (ChiCTR2100053406, ChiCTR2100052858 & ChiCTR2300069244).

Methods:

Patients (6–35 y of age) with TDT were eligible. Peripheral CD34+ HSPCs were collected by apheresis after mobilization with G-CSF and plerixafor. CD34+ cells were edited with CRISPR-Cas9 using a guide RNA specific for the binding site of BCL11A on the *HBG1/2* promoter. Prior to RM-001 product infusion (day 0), patients received myeloablative conditioning with Busulfan from day-7 to day-4. Patients were monitored for stem cell engraftment/hematopoietic recovery, adverse events (AEs), Hb production, HbF and F-cell expression, pRBC transfusion requirements, and on-target allelic editing frequency. After 24-month follow-up, patients will be enrolled into a long-term follow-up study for up to 13 years.

Results:

As of Feb 28, 2024, 16 TDT patients have been treated with RM-001 and followed ≥4 months (Figure). The first 5 subjects have been followed up more than 2 years (24.8-27.7 months). Eleven patients have β0/β0 genotype and five patients have β0/β+ genotype. Patients had received a median of 57.4 units/y pRBC transfusions (range: 39-106.3 units/y) before enrollment.

All subjects received a single dose of RM-001 cells and achieved both neutrophil and platelet engraftments 2 to 3 weeks after RM-001 infusion (neutrophil: day 12-19, platelet: day 10-35). Patients ceased pRBC transfusion at a median of 18.5 days (10-95 days) after RM-001 infusion and remained transfusion-free through the reported period (3.9-27.2 months). All 16 patients reached transfusion-independence (TI, total Hb continued ≥ 9g/dL, started 60 days after last RBC transfusion). Six patients had met the primary efficacy endpoint (TI 12, Hb ≥9 g/dL without RBC transfusion for ≥12 consecutive months) and 6 other patients had reached the key secondary efficacy endpoint (TI 6, Hb ≥9 g/dL without RBC transfusion for ≥6 consecutive months). Averagely, HbF reached ≥9 g/dL at 3 month post-RM-001-infusion and continuously maintained over this level through the reported period and total hemoglobin maintained around 11.5 g/dL (10~13 g/dL) since 4 months after RM-001 treatment.

The safety profile was generally consistent with busulfan myeloablation and autologous hematopoietic stem cell transplantation. No RM-001 related serious adverse event (SAE) report. All of adverse events have been resolved.

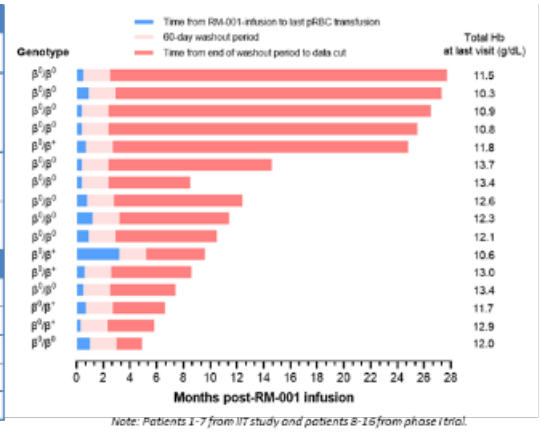
Summary/Conclusion:

All subjects treated with RM-001 demonstrated sustained expression of HbF to a level that means transfusion

independence. The subjects who received RM-001 treatment early have reached the safety and efficacy endpoints. This study provides clinical evidence supporting the safety and efficacy of RM-001 in treating TDT.

Submitted on behalf of the RM-001 Investigators.

Patients Characteristics		N = 16
Gender	Male	7
	Female	9
Age, years, median (range)		16.6 (7.9, 25.6)
6-11 years, n (%)		4 (25.0)
12-17 years, n (%)		7 (43.75)
18-35 years, n (%)		5 (31.25)
Genotype, n (%)	$\beta^0\beta^0$	11 (68.8)
	$\beta^0\beta^+$	5 (31.2)
Pre Study pRBC transfusions, U/y median (range)		57.4 (39, 106.3)
Treatment Characteristics, N = 16		**Median (Range)**
DP dose, CD34+ cells $\times 10^6$/kg		16.9 (7.9, 21.5)
Neutrophil engraftment, study day		15 (12, 19)
Platelet engraftment, study day		21 (10, 35)
Last pBRC transfusion, study day		18.5 (10, 95)
Follow-up, months		11.0 (4.9, 27.7)



Note: Patients 1-7 from IIT study and patients 8-16 from phase I trial.

Keywords: Thalassemia, Clinical data, Gene therapy