

(P1515) SAFETY AND EFFICACY OF RM-001, AUTOLOGOUS HBG1/2 PROMOTER-MODIFIED CD34+ HEMATOPOIETIC STEM AND PROGENITOR CELLS, IN TRANSFUSION-DEPENDENT B-THALASSEMIA

Topic: 27. Thalassemias

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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 $\beta 0/\beta 0$ genotype and five patients have $\beta 0/\beta +$ 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 ≥ 9 g/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.

Copyright Information: (Online) ISSN: 2572-9241

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Abstract Book Citations: Authors, Title, HemaSphere, 2024;8:(S1):pages.

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.

