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POSTER ABSTRACTS

801.GENE THERAPIES

Safety and Efficacy of RM-001 (Autologous HBG1/2 Promoter-modified CD34+ Hematopoietic Stem and Progenitor Cells) in Patients with Transfusion-Dependent β-Thalassemia

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Background:
Reactivating fetal globin (HbF) is a promising treatment for β-hemoglobinopathies. Natural mutations in the promoter region of γ-globin genes (*HBG1/2*) that disrupt the binding of the transcriptional repressors BCL11A could lead to a lifelong persistence of fetal γ-globin expression. 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.

Aims:
ChiCTR2100053406 and ChiCTR2100052858 are ongoing multi-center, first-in-human studies of RM-001 for TDT. Here, we present available safety and efficacy results from 7 patients that have been dosed with RM-001.

Methods:
Patients (6-35 y of age) with TDT receiving packed red blood cell (pRBC) transfusions of ≥100 mL/kg/y or ≥10 units/y in the previous 2ys 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-3. Patients were monitored for stem cell engraftment/hematopoietic recovery, adverse events (AEs), Hb production, HbF and F-cell expression, and pRBC transfusion requirements. Bone marrow cells were obtained at 3, 6, 12 and 24 months after RM-001 infusion to measure the on-target allelic editing frequency using next-generation sequencing.

Results:
Data presented here for 7 TDT patients have been treated with RM-001. As of July 31, 2023, patients were followed up from 1 to 20 months and 5 of them have been followed up more than 15 months. Six patients have β^0/β^0 genotype (CD17/CD41-42, n=1; CD41-42/CD41-42, n=5) and the other has β^0/β^+ genotype (CD41-42/IVS-II-654). In addition to β-thalassemia (CD41-42/CD41-42), two patients also carry a Southeast Asian deletion of α-globin genes ($-^{SEA}/\alpha\alpha$). Patients had received a mean of 55.8 units/y pRBC transfusions (range: 39-79.6 units/y).
All patients 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 11-19, platelet: day 10-22). All patients ceased pRBC transfusions within 1 month after RM-001 infusion and remained transfusion-free through the reported period (Figure). For the 6 patients that have been followed up more than 6 months, HbF reached 9g/dL at 4 month post-RM-001 infusion and continuously maintained over this level through the reported period. From 6 month post-RM-001 infusion, hemoglobin in all patients consists of HbF (97.6%-99.8%) and HbA2 only, including the fifth patient who has a $\beta 0/\beta+$ genotype (99.5% HbF). Five participants have remained transfusion

independent more than 15 months and the mean HbF in the first 4 patients was 11g/dL(10.9-11.3 g/dL) at 18 month post-RM-001 infusion.
The safety profile was generally consistent with busulfan myeloablation and autologous hematopoietic stem cell transplantation. No RM-001 related SAE report.

Summary/Conclusion:

This updated data reported here from 7 patients with TDT infused with RM-001 demonstrated clinically meaningful increases in total hemoglobin (Hb) and HbF levels. All patients stopped receiving pRBC transfusions within 1 month after RM-001 infusion and remained transfusion-free through the time of this analysis. The safety profile of RM-001 is generally consistent with myeloablative conditioning and autologous hematopoietic stem cell transplantation. These results strongly support continued investigation of RM-001 as a potential cure for patients with TDT.
Data will be updated for the presentation.
Submitted on behalf of the RM-001 Investigators.

Disclosures No relevant conflicts of interest to declare.

Patients and Disease Characteristics							
Patient No	1	2	3	4	5	6	7
Gender	M	F	M	F	F	M	F
Age (y)	9.8	13.7	8	7.9	17.6	25.6	16.9
Genotype	CD17/ CD41-42	CD41-42/ CD41-42	CD41-42/ CD41-42	CD41-42/ CD41-42	CD41-42/ IVS-II-654	CD41-42/ CD41-42 $--^{SEA}/\alpha\alpha$	CD41-42/ CD41-42 $--^{SEA}/\alpha\alpha$
Pre Study pRBC transfusions, U/y	39	54.8	50.3	48.5	64.9	79.6	53.5
Treatment Characteristics							
DP dose, CD34+ cells $\times 10^6$/kg	17.3	13	20.2	19.5	17.3	9.0	10.1
Neutrophil engraftment[a], Study day[b]	19	16	14	17	13	15	11
Platelet engraftment[c], Study day	21	21	16	15	10	22	12
Last pBRC transfusion, Study day	15	28	11	13	20	11	11
pBRC transfusions after DP infusion, U	6.5	7.5	3	4	3.5	8.5	4
PLT transfusions after DP infusion, U	2	4	3	2	1	11	0

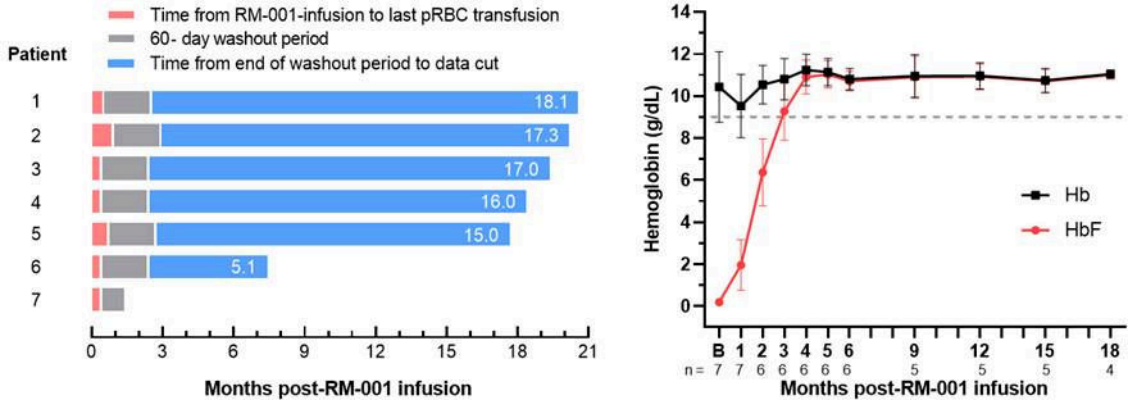

Figure 1

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