P1465 INITIAL SAFETY AND EFFICACY STUDY OF RM-001, AUTOLOGOUS HBG1/2 PROMoter-MODIFIED CD34+ HEMATOPOIETIC STEM AND PROGENITOR CELLS, IN TRANSFUSION-DEPENDENT BETA-THALASSEMIA

**Topic:** 25. Gene therapy, cellular immunotherapy and vaccination - Clinical

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**Background:** Natural mutations that cause hereditary persistence of fetal hemoglobin (HPFH) alleviate the symptoms of β-thalassemia. It is now known that small natural deletions and mutations in the γ-globin gene (HBG1/HBG2) promoters disrupt the binding of the transcriptional repressors BCL11A, causing HPFH. Using gene editing to mimic these mutations should reactivate γ-globin in patients with transfusion-dependent β-thalassemia (TDT) and ameliorate the debilitating effects of mutations in β-globin.

**Aims:** To induce HbF production in erythrocytes, we used ex vivo CRISPR-Cas9–based gene editing to modify HBG1/HBG2 promoter in hematopoietic stem and progenitor cells (HSPCs), producing RM-001. We initiated initial safety and efficacy study of RM-001 in TDT patients. Here, we present initial results from the first 2 patients treated 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 2 y 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/HBG2 promoter. Prior to RM-001 DP infusion, 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, pRBC transfusion requirements.

**Results:** Data presented here for the first 2 TDT patients treated with RM-001. Both patients have β⁰/β⁰ genotype (CD17/CD41-42, CD41-42/CD41-42), with an annualized packed red blood cell (pRBC) transfusion history of 39 units/y and 54.8 units/y over 2 y prior to consent, respectively. Both patients received a single dose of RM-001 cells, ceased pRBC transfusions within 1 month after RM-001 infusion and remained transfusion-free through the reported period. The first patient (CD17/CD41-42, 9 y) achieved neutrophil and platelet engraftment on Day(D+19) and D+21; the other (CD41-42/CD41-42, 13 y) achieved neutrophil and platelet engraftment on D+16 and D+21, respectively. No serious adverse event (SAE) occurred. The safety profile was generally consistent with busulfan myeloablation and autologous hematopoietic stem cell transplantation. Total Hb, HbF and F-cell percentage increased over time in both patients (Figure). Both patients received 6 units of pRBC before transfusion independent (TI) achieved (Hb stably ≥ 90g/L), with last pRBC transfusion on D+15 and D+28, respectively. The first patient achieved TI on D+28 and the other achieved TI on D+39. At 3 month post-RM-001 infusion, total Hb exceed 110 g/L in both patients, with 97-98 g/L HbF. Approximately 89% peripheral erythrocytes are F-cells at 3 month post-RM-001 infusion (Figure). Data will be updated for the presentation.
Summary/Conclusion: The first 2 patients treated with RM-001 demonstrated successful engraftment and both have been transfusion free within two month. Although both patients have β°/β° genotype, they ceased pRBC transfusions within 1 month after RM-001 infusion and remained transfusion-free through the reported period. This is the first-in-human study of autologous HBG1/2 promoter-modified CD34+ HSPCs (RM-001) in TDT and both patients were treated successfully without SAE. Our studies provide novel and initial clinical evidence supporting the safety and efficacy of RM-001 for treating TDT.