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

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Abstract : Background: Beta-Thalassemia is caused by reduced (β+) or absent (β0) synthesis of the β-globin chains of hemoglobin. Transfusions and oral iron chelation therapy have improved the quality of life for patients with Transfusion-Dependent thalassemia (TDT). Recent advances in genome editing platforms of CRISPR-Cas9 have paved the way for induction of HbF by reactivating expression of γ-chain.Aims: We performed CRISPR-Cas9-mediated genome editing of hematopoietic stem cells to mutate HBG1/HBG2 promoter sequence, thereby representing a naturally occurring HPFH-liked mutation, producing RM-001. Here, we present an initial assessment of safety and efficacy of RM-001 in patients with TDT. 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. 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 AEs Hb expression.Results: Data cut as of 28 Feb 2024, 16 TDT patients have been treated with RM-001 and followed ≥3 months. 5 of these 16 patients had finished their 24 months follow up. Eleven patients have β0/β0 genotype and five patients have β0/β+ genotype. In addition to β-thalassemia, two patients had α-deletion with the genotype of --/αα. Efficacy:All patients received a single dose intravenous infusion of RM-001 cells. 5 of them had been followed 24 months or longer. All patients achieved transfusion-independent (TI, total Hb continued ≥ 9g/dL) (Figure1). Patients demonstrated sustained and clinically meaningful increases in HbF levels since 4 month post-RM-001 infusion (Figure.2). Total hemoglobin in all patients was stable at 10-12g/dL during the follow-up period. Safety:The adverse events observed after RM-001 infusion were consistent with those that are typical of Busulfan-based myeloablation. The allelic editing analysis at 6-month visit showed that the on-target allelic editing frequency in bone marrow cells was 73.44% (64.65% to 84.6%, n=13).Summary/Conclusion: This interim analysis, in which all the 19 patients age from 7.9 to 25yo met the success criteria for the trial with respect to transfusion independence, showed that autologous HBG1/2 promoter-modified CD34+ HSPCs gene therapy resulted in an adequate amount of HbF as early as 2 months after infusion led to near-normal hemoglobin levels, remained transfusion-free through the reported period without product related SAE. After RM-001 infusion, high levels of HbF proportion and on-target editing in bone marrow cells were maintained. Submitted on behalf of the RM-001 Investigators.

Keywords : thalassemian, genetherapy, CRISPR/Cas9, HbF
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