Abstract: P1514

Title: EFFICACY AND SAFETY OF BRL-101, CRISPR-CAS9-MEDIATED GENE EDITING OF THE BCL11A ENHANCER IN TRANSFUSION-DEPENDENT BETA-THALASSEMIA

Abstract Type: Poster Presentation

Topic: Thalassemias

Background:

β-Thalassemia is an inherited hemolytic disease that is prevalent worldwide. Over 200 mutations in the HBB gene, which encodes adult hemoglobin (HbA), result in β-thalassemia. Hereditary persistence of fetal hemoglobin (HbF) can alleviate the symptoms of anemia. CRISPR-Cas9-mediated disruption of the BCL11A erythroid enhancer results in the reduction of BCL11A expression and the induction of fetal γ-globin, which is a practicable therapeutic strategy for treating transfusion-dependent β-thalassemia (TDT).

Aims:

The purpose of the study is to evaluate the safety and efficacy of a single dose of BRL-101 in subjects ≥3 and ≤35 years of age with TDT.

Methods:

We obtained mobilized autologous CD34+ cells from 9 TDT patients sponsor initiated in phase I/II clinical trial (NCT05577312) and 6 TDT patients in investigator initiated clinical study（NCT04211480, NCT04205435）respectively. These cells were edited with CRISPR-Cas9 RNP at the +58 erythroid specific enhancer region of the BCL11A gene and then reinfused after the patients had undergone myeloablative busulfan conditioning. We subsequently monitored adverse events, neutrophil and platelet engraftment.

Results:

Between October 15, 2019, and August 24, 2023, 15 patients with TDT were enrolled and received BRL-101 with a median age of 11.5 years (6-26). Among all the treated patients, 8 patients were β0/β0 phenotype, 3 patients were β0/β+ phenotype,3 patients were β+/β+ phenotype, and 1 patient was β0/βE phenotype. As of November 27, 2023, the median follow-up was 9.8 months (3.2-43.6 m) (Tab.1). The longest duration of TI was 41.6 months. The levels of mean HbF increased significantly from 2.1 to 150.2 g/L and the mean total hemoglobin inceased from 114.1 to 152.0 g/L after BRL-101 infusion (Fig.1). At 5 months after BRL-101 infusion, the proportion of HbF-expressing red blood cells in peripheral blood had reached 96.5%, and then continued to rise and remained around 98-99% (Fig.2). Treatment-related adverse events were typical of those associated with myeloablation and autologous stem-cell transplantation, mainly manifested as hematological toxicities (Tab.2, Tab.3). 3 patients experienced adverse events (AEs) grade ≥3 which related to BRL-101. 4 patients experienced serious AEs (SAEs), including decreased platelet count, shock, febrile infection, soft tissue infection, and veno-occlusive liver disease. Only decreased platelet count may related to BRL-101, the others were due to busulfan treatment. All the SAEs were resolved. No study drug-related withdrawals or deaths occurred during treatment.

Summary/Conclusion:

Whether genotype was β0/β0 or non-β0/β0, BRL-101 demonstrated clinically meaningful increases in total Hb and HbF which occurred early and have been maintained over time, the safety profile of BRL-101 is generally consistent with that of myeloablative conditioning and autologous hematopoietic stem cell transplant. The updated data with 15 patients reported here are consistent with previous reports and support continued investigation of BRL-101 as a potential functional cure for patients with TDT.

Figure 1. Substantial increases in mean total Hb and HbF level

Figure 2. Mean (range) % peripheral F-cells, % circulating RBCs expressing HbF

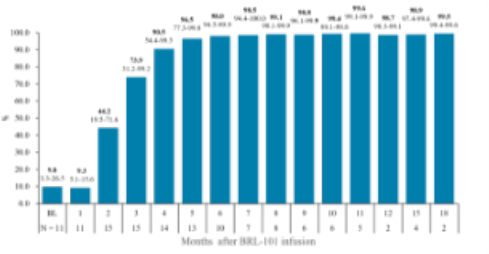

Table 1. Patient Baseline and Treatment Characteristics

Patient characteristics			Treatment characteristics	
Genotype, n	β0 / β0	8	**Drug product cell dose,** CD34+ cells × 10⁶/kg	**Median** (range) 8.63 (3.9-14.8)
	β0 / β+	3		
	β+ / β+	3		
	β0 / βE	1		
Gender, Female/Male, n		7/8	**Neutrophil engraftment** Study Day	19.0 (14-29)
Age at consent, years		11.5 (6.0-25.0)	**Platelet engraftment** Study Day	41.0 (21-165)
Pre-study pRBC transfusions Unit/year, median (range)		36.0 (23.5-95.0)	**Duration of follow-up,** Months	9.8 (3.2-43.6)

Table 2. Safety profile of BRL-101

Post-BRL-101 AEs Overview	**n=15**
Patients with any AEs, n(%)	15 (100%)
Patients with AEs related to BRL-101, n(%)	6 (40.0%)
Patients with SAEs, n(%)	4 (26.7%)
Patients with SAEs related to BRL-101, n(%)	1 (6.7%)
Patients with AEs Grade 3/4, n(%)	15 (100%)
Patients with AEs leading to death, n(%)	0

Table 3. Patients with AEs Grade 3/4 and SAE Sorted by SOC and PT

AEs Grade 3/4 and SAE	**n=15**	**AEs Grade 3/4 and SAE**	**n=15**
Investigations		**Vascular disorders**	
White blood cell count decreased	15 (100%)	Shock*	1 (6.7%)
Platelet count decreased*	15 (100%)	**Metabolism and nutrition disorders**	
Neutrophil count decreased	15 (100%)	Hypokalaemia	4 (26.7%)
Neutrophil percentage decreased	3 (20.0%)	**Respiratory, thoracic and mediastinal disorders**	
Lymphocyte count decreased	2 (13.0%)	Unilateral pleural effusion	1 (6.7%)
Alanine aminotransferase increased	1 (6.7%)	**Vascular disorders**	
Erythrocyte sedimentation increased	1 (6.7%)	Epistaxis	1 (6.7%)
Blood and lymphatic system disorders		**Infections and infestations**	
Febrile neutropenia	3 (20.0%)	Febrile infection*	1 (6.7%)
Anemia	2 (13.3%)	Pneumonia	2 (13.3%)
Gastrointestinal disorders		Infections	1 (6.7%)
Stomatitis	4 (26.7%)	Sepsis (6.7%)	1
Oral bacterial infection	2 (13.3%)	Upper respiratory tract infection*	1 (6.7%)
Tongue thrust	1 (6.7%)	**Skin and subcutaneous tissue disorders**	
Upper gastrointestinal haemorrhage	1 (6.7%)	Soft tissue infection*	1 (6.7%)
Lower gastrointestinal haemorrhage	1 (6.7%)	**Hepatobiliary disorders**	
Psychiatric disorders		Veno-occlusive liver disease*	1 (6.7%)
Dysphoria	1 (6.7%)		
Reproductive system and breast disorders			
Heavy menstrual bleeding	1 (6.7%)		

** Including SAEs (all resolved).*

Keywords: Hematopoietic stem cell, Thalassemia, Gene therapy, Hemoglobinopathy