Long-Term Clinical Outcomes of Lentiglobin Gene Therapy for Transfusion-Dependent β-Thalassemia in the Northstar (HGB-204) Study

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Background:

Patients with transfusion-dependent β-thalassemia (TDT) may experience transfusional iron overload and end-organ damage. While potentially curative, allogeneic hematopoietic stem cell (HSC) transplantation is limited by transplant-related risks and donor availability. Transplantation of autologous CD34+ cells encoding a β^{A-T87Q}-globin gene (LentiGlobin gene therapy for β-thalassemia) may overcome some of these limitations. β^{A-T87Q}-globin is incorporated into adult hemoglobin (Hb), forming gene therapy-derived HbA^{T87Q}, which can be distinguished from other

Hb species. The phase 1/2 Northstar study (HGB-204; NCT01745120) using the original manufacturing process evaluated the safety and efficacy of LentiGlobin in adolescents and adults with TDT (≥100 mL/kg/yr of red blood cells [RBCs] or ≥8 RBC transfusions/yr) and non-β^0/β^0 or β^0/β^0 genotypes.

Methods

HSCs were mobilized with G-CSF and plerixafor and collected via apheresis. CD34+ cells were transduced with BB305 lentiviral vector. After busulfan myeloablation, patients were infused with transduced cells. Primary efficacy endpoints were sustained production of ≥2 g/dL HbA^{T87Q} between months 18 and 24 and transfusion independence (TI; weighted average Hb ≥9 g/dL without RBC transfusions for ≥12 months). Patients were monitored for 2 years and subsequently enrolled in the 13-year long-term follow-up study, LTF-303 (NCT02633943). Results are shown as median (min – max) unless otherwise indicated.

Results:

Eighteen patients were treated (age: 20 [12 – 35] yrs) and followed for 40.7 (29.3 – 53.8) months as of 13 December 2018. In the 2 years prior to enrollment, patients had an annualized transfusion volume of 169.0 (124.0 – 273.0) mL/kg/yr and pre-transfusion weighted mean nadir Hb of 9.3 (7.0 – 10.1) g/dL.

Neutrophil and platelet engraftment occurred at 18.5 (14 – 30) and 39.5 (19 – 191) days, respectively. No patient had graft failure. Grade ≥3 non-hematologic adverse events (AEs) reported in ≥25% of patients after infusion were stomatitis, febrile neutropenia, and pharyngeal inflammation. No replication-competent lentivirus or death has been reported. The vector integration site profile in all 18 patients has remained polyclonal. The number of unique integration sites (UIS) identified was 1646 (190 – 2888), 1677 (151 – 6935), 2484 (984 – 5511), 1773 (1260 – 2693) at Months 12 (n=18), 24 (n=18), 36 (n=11), 48 (n=4), respectively. The highest mean (SD) frequency of any UIS in patients across all visits was 11.5% (5.8%). No oncogenesis has been reported.

In Northstar, 16/18 (89%) patients achieved the primary endpoint of ≥2 g/dL HbA^{T87Q} between months 18 and 24. Eight of 10 (80%) patients with non-β^0/β^0 genotypes achieved and maintained TI; current duration of TI was 38 (21.2 – 45.3) months (**Figure 1**). The weighted average total Hb during TI was 10.3 (9.1 – 13.2) g/dL. Total Hb and HbA^{T87Q} remained stable over time. Total Hb in patients with non-β^0/β^0 genotypes who achieved TI was 10.3, 10.4, 10.6, and 11.1 g/dL at Months 12 (n=8), 24 (n=8), 36 (n=7), 48 (n=3), respectively. Transfusion volumes were reduced by 73% and 43% in the 2 patients still receiving transfusions.

Three of 8 (38%) patients with β^0/β^0 genotypes achieved TI with a current duration of 16.4 (16.1 – 20.8) months. Weighted average total Hb during TI was 9.9 (9.5 – 10.1) g/dL and HbA^{T87Q} was 8.0 – 8.9 g/dL at last visit. One additional patient was transfusion-free for 13.7 months; however,

total Hb was <9 g/dL. The 4 other patients had a transfusion volume reduction of 53% (10% – 72%).

Patients who achieved TI resumed iron chelation 13 (2 – 15) months after infusion and all remain on iron chelation as of last follow-up. Serum ferritin and liver iron content (LIC) (**Figure 2A, 2B**) were reduced in patients who achieved TI by 55% (16 – 78%) and 56% (38 – 83%) from screening to Month 48 (n=4), respectively. Of these 4 patients who had a Month 48 visit, LIC values were 0.8 – 7.1 mg/g at Month 48 compared to 4.8 – 11.5 mg/g at screening. In patients who achieved TI, cardiac T2* ranged from 27.0 – 39.0 msec at screening and 31.4 – 57.6 msec at last visit.

Summary:

With up to 4.5 years of follow-up after LentiGlobin gene therapy, generally stable HbA^{T87Q} levels and durable TI were observed in 8/10 and 3/8 patients with TDT and non-β^0/β^0 and β^0/β^0 genotypes, respectively. Iron burden has improved over time in patients who achieved TI. The safety profile of LentiGlobin remains consistent with myeloablative conditioning.