Northstar-2: Updated Safety and Efficacy Analysis of Lentiglobin Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia and Non-β0/β0 Genotypes

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Background:

Transfusion-dependent β-thalassemia (TDT) is treated with regular, lifelong red blood cell (RBC) transfusions and despite iron-chelating therapy, carries a risk of serious organ damage from iron overload and other complications. Transplantation with autologous CD34+ cells encoding a β^{A-T87Q}-globin gene (LentiGlobin for β-thalassemia) is being evaluated in patients with TDT. Interim results are presented here from the ongoing, international, single-arm, phase 3 Northstar-2 study (HGB-207; NCT02906202) of LentiGlobin gene therapy in pediatric, adolescent, and adult patients with TDT (defined by receiving ≥100 mL/kg/yr of RBCs or ≥8 RBC transfusions/yr) and non-β^0/β^0 genotypes.

Methods:

Patients undergo hematopoietic stem cell (HSC) mobilization with G-CSF and plerixafor. Following apheresis, CD34+ cells are transduced with BB305 lentiviral vector and infused into patients after pharmacokinetic-adjusted, single-agent busulfan myeloablation. The primary efficacy endpoint is transfusion independence (TI; weighted average hemoglobin [Hb] ≥9 g/dL without RBC transfusions for ≥12 months). HSC engraftment, β^{A-T87Q}-globin expression, Hb levels, detection of replication competent lentivirus (RCL), and adverse events (AE) are also assessed. Patients are followed for 2 years and offered participation in a long-term follow-up study. Summary statistics are presented as median (min – max).

Results:

Twenty patients were treated in Northstar-2 as of 13 December 2018 and have been followed for a median of 8.1 (0.5 – 22.2) months. At enrollment, median age was 16 (8 – 34) years; 5 patients were <12 years of age. Median drug product cell dose was 8.0 (5.0 – 19.9) $x10^6$ cells/kg and vector copy number was 3.2 (1.9 – 5.6) copies/diploid genome. Time to neutrophil and platelet engraftment in the 18/20 and 15/20 evaluable patients was 22.5 (13 – 32) and 45 (20 – 84) days, respectively.

Non-hematologic grade ≥3 AEs in ≥3 patients after LentiGlobin infusion included stomatitis (n=12), febrile neutropenia (n=6), pyrexia (n=4), epistaxis (n=3), and veno-occlusive liver disease (n=3). One serious AE of grade 3 thrombocytopenia was considered possibly related to LentiGlobin. No patient died, had graft failure, or had detection of RCL. No insertional oncogenesis has been observed.

Gene therapy-derived HbA^{T87Q} stabilized approximately 6 months after infusion. In adolescent and adult patients treated with LentiGlobin, median HbA^{T87Q} at Months 6, 12 and 18 was 9.5 (n=11), 9.2 (n=8), and 9.5 (n=3) g/dL, respectively. The median total Hb without transfusions at Months 6, 12, and 18 were 11.9 (n=11), 12.4 (n=8), 12.3 (n=2) g/dL, respectively. At Month 6, 91% (10/11) of patients had total Hb of >11 g/dL without transfusions.

Five adolescent and adult patients were evaluable for the primary endpoint of transfusion independence, 4 (80%) of whom achieved TI. The median weighted average Hb during TI was 12.4 (11.5 – 12.6) g/dL which compared favorably to pre-transfusion nadir Hb levels before enrollment (median 9.1 g/dL [7.5 – 10.0 g/dL]). At time of analysis, the median duration of TI was 13.6 (12.0 – 18.2) months. One patient who did not achieve TI stopped transfusions for 11.4 months but resumed transfusions due to recurrent anemia. This patient had a 71.4% reduction in RBC transfusion volume from Month 6 to Month 18 compared to baseline.

Marrow cellularity and myeloid:erythroid (M:E) ratios were evaluated in 8 adolescent and adult patients with ≥12 months follow-up to assess the effect of LentiGlobin treatment on dyserythropoiesis. Seven of 8 patients had improved marrow M:E ratios at Month 12 (0.63 – 1.90)

compared with baseline (0.14 – 0.48). In patients who stopped transfusions, soluble transferrin receptor levels were reduced by a median of 72% (58% – 78%) at Month 12 (n=6). Updated outcomes in adolescents and adults and outcomes in pediatric patients will be reported.

Summary:

In this update of the Northstar-2 study of LentiGlobin gene therapy in patients with TDT and non-β^0/β^0 genotypes, transfusion independence was observed in 4/5 evaluable adolescent and adults and 10/11 treated patients had total Hb of >11 g/dL without transfusion support 6 months after LentiGlobin infusion. HbA^{T87Q} stabilized approximately 6 months after treatment and patients who stopped RBC transfusions had improved erythropoiesis. A safety profile consistent with busulfan conditioning was observed after LentiGlobin gene therapy.