Northstar-2: Updated Safety and Efficacy Analysis of LentiGlobin Gene Therapy in Patients with Transfusion-dependent β-Thalassemia and Non-β^0/β^0 Genotypes

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BACKGROUND

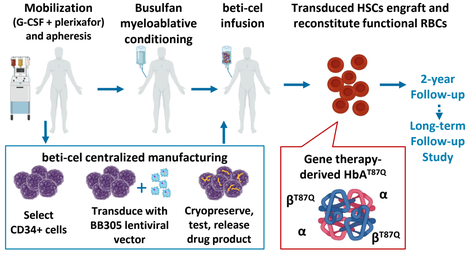
- Transfusion-dependent β-thalassemia (TDT) is treated with regular, lifelong red blood cell (RBC) transfusions and iron chelation.
  - Despite the optimization of this approach, many patients have significant complications mainly deriving from iron overload.
- Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be curative, but it is limited by donor availability and is associated with transplant-related risk
  - Many patients are not considered optimal candidates due to lack of an HLA-matched donor, disease complications, and/or age
- Autologous gene therapy with betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) is being evaluated in patients with TDT and non-β^0/β^0 genotypes in the phase 3 Northstar-2 study (HGB-207; NCT02906202)

METHODS & STUDY DESIGN

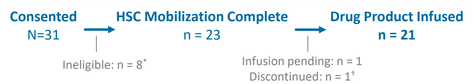
Key eligibility criteria
- TDT: ≥ 100 mL/kg/yr of RBCs or ≥ 8 RBC transfusions/yr
- Non-β^0/β^0 genotype
- ≤ 50 years of age

Primary endpoint: Transfusion independence (TI; Weighted average hemoglobin (Hb) ≥ 9 g/dL without RBC transfusions for ≥ 12 months)

Key secondary endpoints
- Characterization of transfusion independence
- Total Hb over time
- Assessment of improvement in ineffective erythropoiesis



STUDY DISPOSITION



*Reason for ineligibility: 3 withdrew consent, 3 screen failures due to advanced liver disease, 1 screen failure due to cardiac magnetic resonance imaging, 1 due to ineligible genotype; †Patient discontinued because of positive pregnancy test result

- **Median follow-up: 11.6 months** (min – max: 0.9 – 26.3 months)
- Target enrollment: 23 patients
- Data is reported as of June 12, 2019

RESULTS

Table 1. Drug product characteristics

	N = 21 **median** (min – max)
Vector copy number, vector copies/diploid genome	**3.3** (1.9 – 5.6)
CD34+ cells transduced, %	**78.0** (34.0 – 90.0)
Cell dose, x 10^6 CD34+ cells/kg	**7.9** (5.0 – 19.9)

- Patients received single-agent myeloablative busulfan conditioning
  - Daily average estimated busulfan AUC over 4 days: 4428 µM*min (min – max: 3709 – 8947 µM*min)

Table 2. Engraftment characteristics

	N = 21 **median** (min – max)
ANC ≥ 500 cells/µL x 3 days, days	**23.0** (13.0 – 32.0)
Platelets ≥ 20,000 cells/µL, days	**46.0** (20.0 – 94.0)

ANC, absolute neutrophil count

- 91% (10/11) of patients had platelets ≥ 100x10^9/L at Month 12 compared to 83% (15/18) of patients in HGB-204
  - One patient in HGB-207 only achieved platelets ≥ 100x10^9/L at Month 15

RESULTS

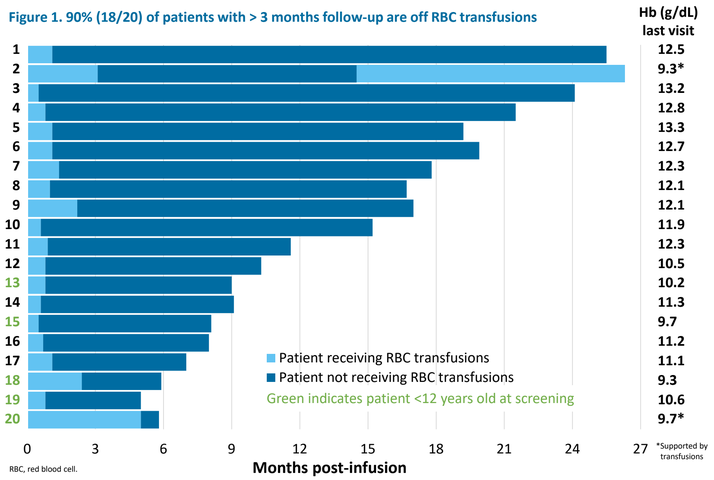
Table 3. Patient characteristics

Demographics		N = 21 n (%)
Genotype n, (%)	β^+/β^0 β^E/β^0 β^+/β^+	**10.0** (47.6) **6.0** (28.6) **5.0** (23.8)
Age at consent, median (min – max), yr		**15.0** (8.0 – 34.0)
< 12 years old, n (%)		**6.0** (28.6)
≥ 12 – < 18 years, n (%)		**6.0** (28.6)
≥ 18 years, n (%)		**9.0** (42.9)
Pre-study pRBC transfusion history Retrospective data 2 years prior to enrollment		**median** (min – max)
Volume, mL/kg/yr		**193.6** (142.1 – 274.4)
Number, n/yr		**17.0** (11.5 – 37.0)
Pre-transfusion Hb, g/dL		**9.6** (7.5 – 11.0)

Hb, hemoglobin; pRBC, packed red blood cells

- Select comorbidities at enrollment:
  - Iron overload/chelation therapy (n=21)
  - Vitamin D deficiency (n=5)
  - Osteoporosis/osteopenia (n=4)
  - Splenectomy (n=4)
  - Below normal height (n=2)
  - Extramedullary hematopoiesis (n=2)
  - Hemosiderosis (n=2)
  - Hypogonadism (n=2)

Figure 1. 90% (18/20) of patients with > 3 months follow-up are off RBC transfusions



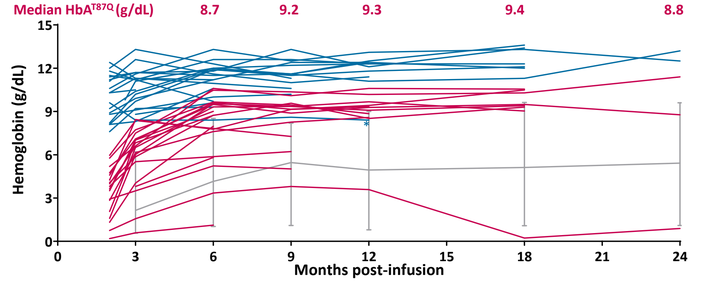
RBC, red blood cell.

Primary Endpoint: 9/10 (90%) evaluable patients achieved transfusion independence (TI)
- **Characteristics of TI (**Weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months [median; min – max])
  - **Time to last transfusion: 1.1 months** (0.5 – 2.2 months)
  - **Duration: 15.2 months** (12.1 – 21.3 months); all responses are ongoing
  - **Weighted average Hb: 12.2 g/dL** (11.4 – 12.8 g/dL)

Iron management after beti-cel treatment
- 5 patients received phlebotomy for iron reduction
- 8 patients re-started iron chelation therapy, including two patients who have since stopped chelation

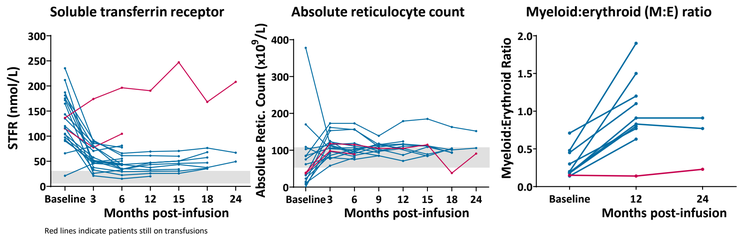
Figure 2. Stable total hemoglobin and gene therapy-derived HbA^{T87Q} in the majority of patients

	M6 (N=17)	M9 (N=14)	M12 (N=11)	M18 (N=8)	M24 (N=3)
Median Total Hb (g/dL)	11.5	11.6	12.3	12.2	12.5
Median HbA^{T87Q} (g/dL)	8.7	9.2	9.3	9.4	8.8



*Last Hb before patient 2 restarted red blood cell transfusions; Median total Hb values include Patient 2 who was on transfusions; Hb, hemoglobin

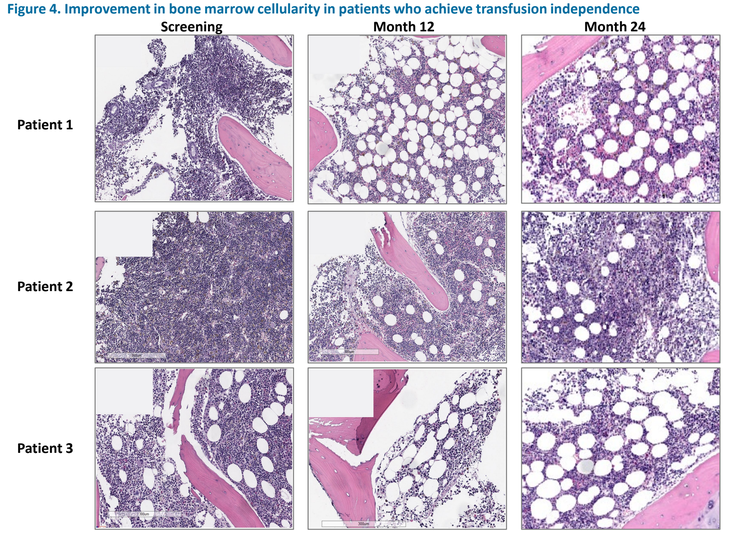
Figure 3. Improvement in markers of dyserythropoiesis in patients who stopped transfusions



Red lines indicate patients still on transfusions

- Soluble transferrin receptor and reticulocytes trend toward normal in patients who have stopped transfusions
- Patients who achieve transfusion independence show an improved M:E ratio

Figure 4. Improvement in bone marrow cellularity in patients who achieve transfusion independence



- Patients 1 and 3 who achieved transfusion independence had improved bone marrow at Months 12 and 24 while Patient 2 who did not achieve TI did not have an improvement in bone marrow histology

Figure 5. Positive correlation between drug product vector copy number (VCN) and peripheral VCN and HbA^{T87Q}

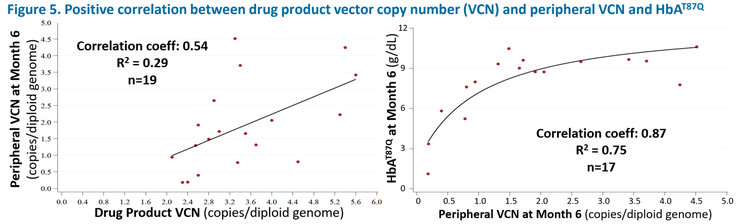
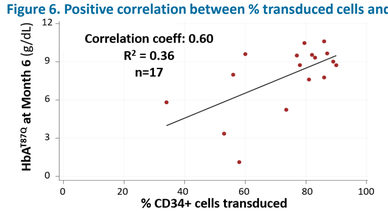


Figure 6. Positive correlation between % transduced cells and HbA^{T87Q}



- Drug product VCN positively correlates with peripheral VCN levels at Month 6
- Peripheral VCN at Month 6 and the percentage of transduced CD34+ cells in the drug product positively correlate with HbA^{T87Q} levels at Month 6

Table 4. Safety profile of beti-cel remains generally consistent with that of myeloablative busulfan conditioning

Non-hematologic Grade ≥ 3 AEs* Post beti-cel infusion in ≥ 3 patients	N = 21 n (%)
Stomatitis	12 (57)
Febrile neutropenia	7 (33)
Epistaxis	3 (14)
Pyrexia	3 (14)
Veno-occlusive liver disease	3 (14)
Serious AEs Post beti-cel infusion in ≥ 1 patient	
Veno-occlusive liver disease	3 (14)
Thrombocytopenia	2 (10)
Contusion	1 (5)
Device-related infection	1 (5)
Febrile neutropenia	1 (5)
Hypotension	1 (5)
Hypoxia	1 (5)
Lower respiratory tract infection	1 (5)
Neutropenia	1 (5)
Neutropenic sepsis	1 (5)
Pyrexia	1 (5)
Sepsis	1 (5)
Stomatitis	1 (5)
Transfusion reaction	1 (5)

*Hematologic AEs commonly observed post-transplantation have been excluded; AE, adverse event

- Adverse events (AEs) considered related or possibly related to the drug product:
  - Prolonged thrombocytopenia (n=2, Grade 3, one AE was serious)
  - Abdominal pain (n=1, Grade 1)
  - Pain in extremity (n=1, Grade 1)
- 3/21 patients experienced liver veno-occlusive disease (VOD) (all Grade 4)
  - All patients recovered following treatment with defibrotide
  - 16/21 patients received VOD prophylaxis
    - 12, ursodiol alone; 3, ursodiol + defibrotide; 1, defibrotide alone
- No graft failure
- All patients are alive
- No complications related to the lentiviral vector including replication-competent lentivirus, clonal dominance

SUMMARY

- Betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy is being evaluated in patients with transfusion-dependent β-thalassemia and a non-β^0/β^0 genotype.
- 90% (9/10) of evaluable patients achieved the primary endpoint of transfusion independence (TI) with stable hemoglobin.
  - Median weighted average Hb during TI: 12.2 g/dL
  - Ongoing duration of TI: 12.1 – 21.3 months
- 90% (18/20) of patients with ≥ 3 months of follow-up no longer require RBC transfusions.
- Patients who stopped RBC transfusions showed improvement in erythropoiesis.
- The safety profile of beti-cel remains generally consistent with that of myeloablative busulfan conditioning.
  - Three serious events of liver veno-occlusive disease occurred.
  - One SAE of grade 3 thrombocytopenia was considered possibly related to beti-cel.
  - 10/11 patients had platelets > 100k at Month 12.
- Further follow-up will continue to assess the long-term efficacy and safety of beti-cel in patients with TDT and a non-β^0/β^0 genotype.

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DISCLOSURES

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