Results from Northstar and Northstar-2 Studies of LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassemia and Non-β^0/β^0 Genotypes

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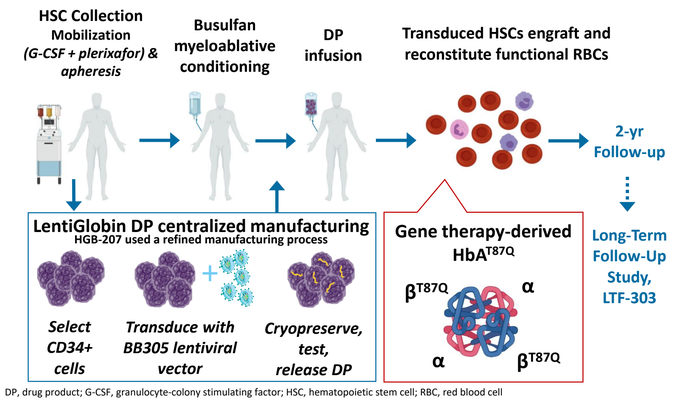
BACKGROUND

- Transfusion-dependent β-thalassemia (TDT) is treated with lifelong supportive care with regular blood transfusions to mitigate anemia, suppress ineffective erythropoiesis, and extend survival.[1,2]
- While potentially curative, allogeneic hematopoietic stem cell (HSC) transplantation is limited by donor availability and transplant-related risks.
- Patients with TDT may benefit from gene therapy involving the addition of a modified β-globin gene to HSCs *ex vivo*, to produce functional hemoglobin (Hb).
- Transplantation of autologous CD34+ cells encoding a $\beta^{A\text{-}T87Q}$-globin gene (LentiGlobin gene therapy for β-thalassemia) is being investigated in clinical studies of patients with TDT.
- **Northstar (HGB-204; NCT01745120):** an international, multi-center, Phase 1/2, open-label, single-arm study of LentiGlobin gene therapy in adolescent and adult patients with TDT and non-β^0/β^0 or β^0/β^0 genotype.[3]
- **Northstar-2 (HGB-207; NCT02906202):** an international, multi-center, Phase 3, open-label, single-arm study of LentiGlobin gene therapy in pediatric, adolescent, and adult patients with TDT and non-β^0/β^0 genotype.
- This poster reports the results of LentiGlobin gene therapy in patients with TDT and non-β^0/β^0 genotype in the Northstar and Northstar-2 studies.

METHODS

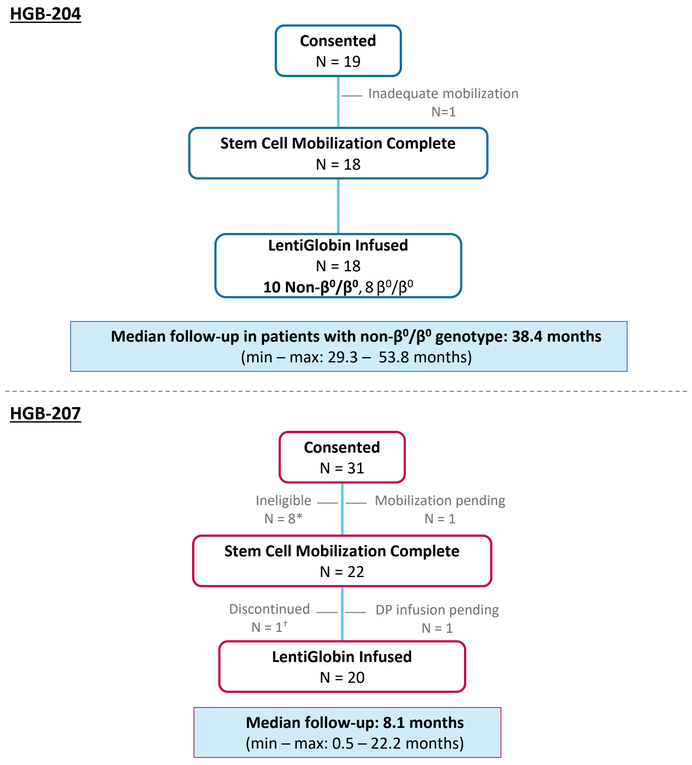
- Patients aged 12 to 35 years in Northstar (HGB-204) and <50 years in Northstar-2 (HGB-207) with TDT (≥100 mL/kg/year of red blood cells [RBCs] or ≥8 RBC transfusions/year) were enrolled.
- Autologous CD34+ cells were mobilized using G-CSF and plerixafor, collected by apheresis, and were transduced with BB305 lentiviral vector.
- Patients underwent single-agent busulfan myeloablative conditioning and were infused with the transduced cells.
- Patients were monitored for safety and efficacy for 2 years and were offered participation in the long-term follow-up study, LTF-303 (NCT02633943).
- **The primary endpoints in Northstar (HGB-204):** the proportion of patients with sustained production ≥2 g/dL of HbA^{T87Q} 18 – 24 months post-infusion and transfusion independence (TI; weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months).
- **The primary endpoint in Northstar-2 (HGB-207):** transfusion independence
- Data presented is as of 13 December 2018

Figure 1. HGB-204 and HGB-207 Study design



DP, drug product; G-CSF, granulocyte-colony stimulating factor; HSC, hematopoietic stem cell; RBC, red blood cell

Figure 2. HGB-204 and HGB-207 Study disposition



*Reason for ineligibility: 3 withdrew consent, 4 screen failures due to advanced liver disease, 1 due to ineligible genotype
†Patient discontinued due to positive pregnancy test

Table 1. HGB-204 and HGB-207 Patient characteristics

		HGB-204 (N = 10)	HGB-207 (N = 20)
Genotypes	β^+/β^0	**1** (10)	**10** (50)
	β^E/β^0	**6** (60)	**6** (30)
	β^+/β^+	**2** (20)	**4** (20)
	Other	**1** (10)	–
Age at consent median (min – max), yr		**19.5** (16 – 34)	**16** (8 – 34)
Pre-study pRBC transfusion volume annualized median (min – max), mL/kg/yr		**151** (140 – 234)	**200.8** (152 – 274)
Liver iron concentration median (min – max), mg/g		**5.7** (1.2 – 26.4)	**5.5** (1 – 41)
Cardiac T2* median (min – max), msec		**37.5** (27 – 54)	**36.5** (20.6 – 50.9)
Splenectomy, n (%)		**3** (30)	**4** (20)

ANC, absolute neutrophil count; AUC, area under the curve; pRBC, packed red blood cells

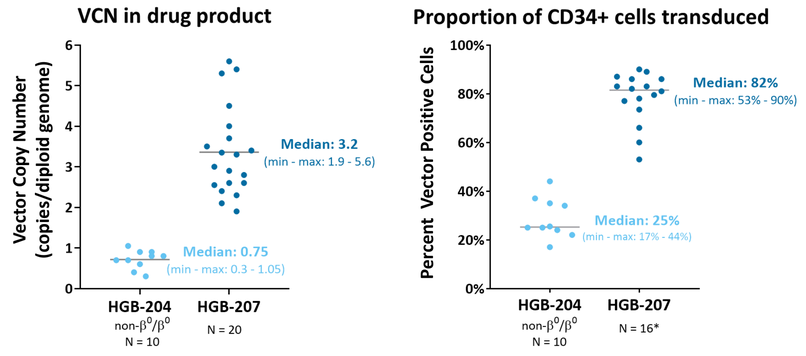
Table 2. HGB-204 and HGB-207 Treatment characteristics

	HGB-204 (N = 10) median (min – max)	HGB-207 (N = 20) median (min – max)
Busulfan AUC estimated average x 4 days, μM*min	**4060** (3030 – 4417)	**4471**† (3709 – 8947)
Neutrophil engraftment ANC ≥500 cells/μL x 3 days, days	**18.5** (14 – 27)	**22.5**‡ (13 – 32)
Platelet engraftment platelets >20k/μL, days	**50.5** (19 – 191)	**45**^ (20 – 84)

†N = 19, Busulfan AUC was not available for 1 patient as of datacut.
‡N = 18, 2 patients with <1 month of follow-up had not engrafted as of datacut.
^N = 15, 5 patients with <1 – 4.9 months of follow-up had not engrafted as of datacut.
AUC, area under the curve.

RESULTS

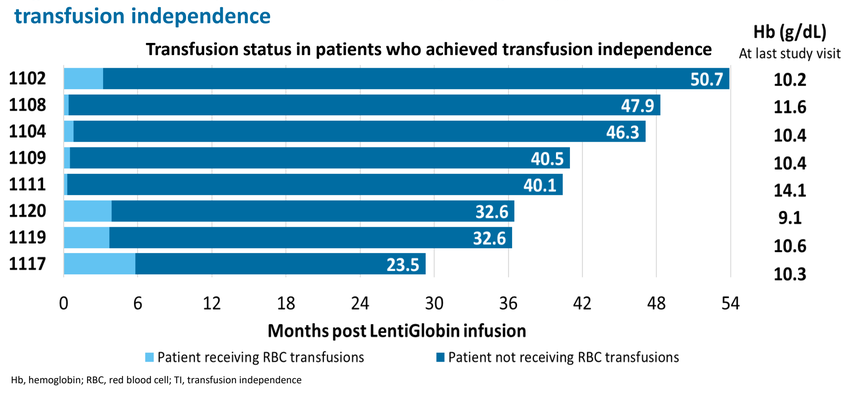
Figure 3. Refined manufacturing yielded more favorable drug product characteristics



*Four % vector positive values were not available at time of datacut
VCN, vector copy number

- **Median cell dose in HGB-204: 7.1 x10^6 CD34+ cells/kg** (min – max: 5.2 – 13.0 x10^6 CD34+ cells/kg)
- **Median cell dose in HGB-207: 8.0 x10^6 CD34+ cells/kg** (min – max: 5.0 – 19.9 x10^6 CD34+ cells/kg)

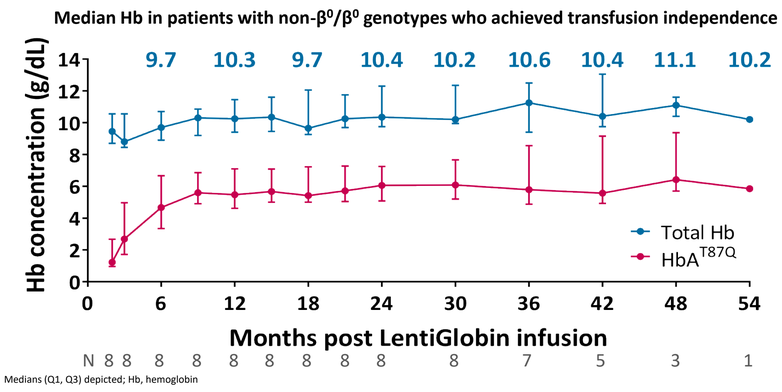
Figure 4. HGB-204: 8/10 patients with non-β^0/β^0 genotypes achieved and maintained transfusion independence



Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence

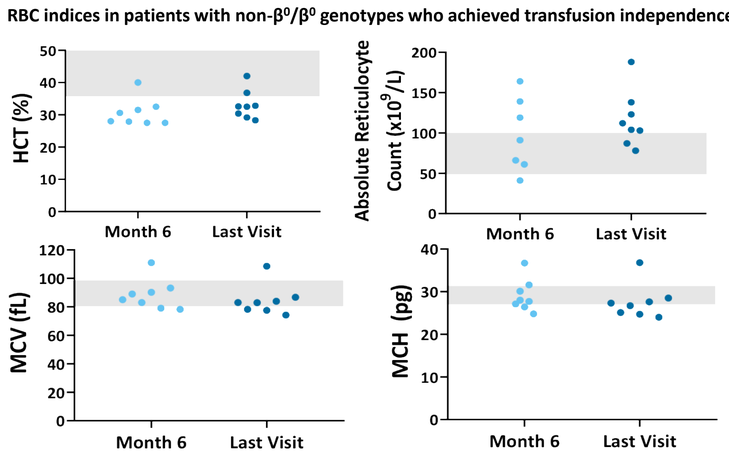
- **Median duration of transfusion independence: 38.0 months** (min – max: 21.2 – 45.3 months); responses are ongoing.
- **Median weighted average Hb during transfusion independence: 10.3 g/dL** (min – max: 9.3 – 13.2 g/dL).

Figure 5. HGB-204: HbA^{T87Q} expression is stable following LentiGlobin through 4 years and beyond



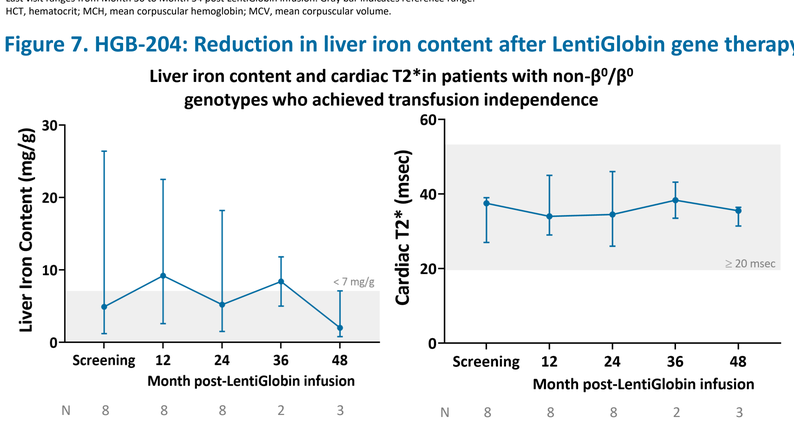
Medians (Q1, Q3) depicted; Hb, hemoglobin

Figure 6. HGB-204: RBC indices were generally normal with transfusion independence



Last visit ranges from Month 36 to Month 54 post LentiGlobin infusion. Gray bar indicates reference range.
HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.

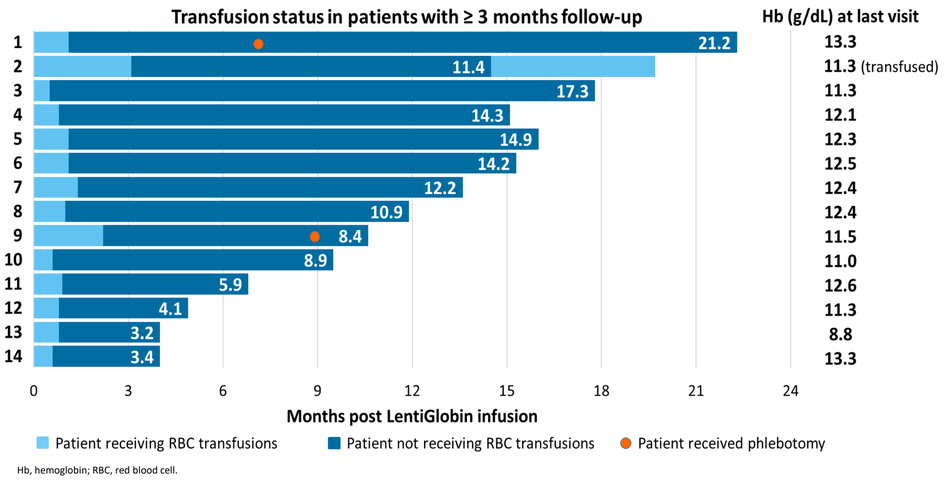
Figure 7. HGB-204: Reduction in liver iron content after LentiGlobin gene therapy



Medians (min, max) depicted.

- Patients re-initiated iron chelation therapy a median of 13 months after LentiGlobin infusion (min – max: 2 – 15 months).

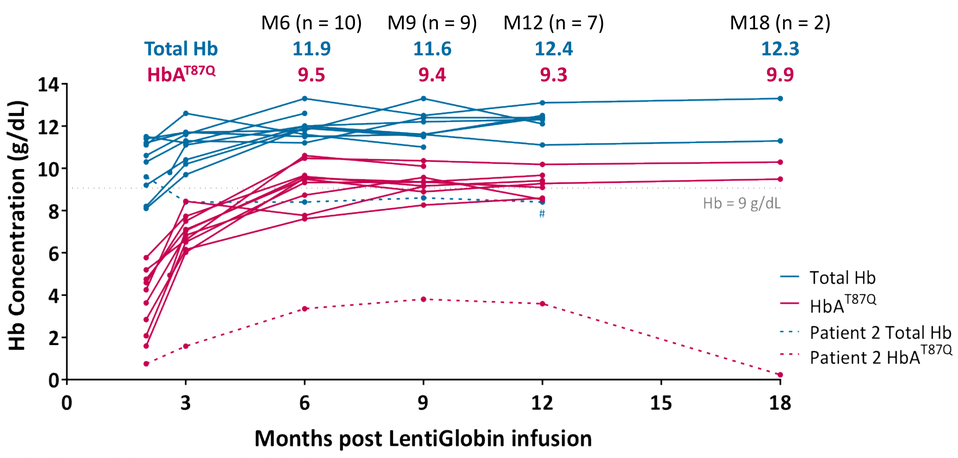
Figure 8. HGB-207: 13/14 patients with ≥ 3 months follow-up are transfusion free



Hb, hemoglobin; RBC, red blood cell.

- **4/5 (80%) evaluable patients achieved the primary endpoint of transfusion independence**
- **Median duration of transfusion independence: 13.6 months** (min – max: 12.0 – 18.2 months).
  - All responses are ongoing.
- **Median weighted average Hb during transfusion independence of 12.4 g/dL** (min – max: 11.5 – 12.6 g/dL).

Figure 9. HGB-207: Stable total Hb and gene therapy-derived HbA^{T87Q} in 10/11 patients with ≥ 6 months follow-up



#Last Hb before patient 2 restarted red blood cell transfusions; Hb, hemoglobin.

Figure 10. HGB-207: Improvement in erythropoiesis after LentiGlobin infusion

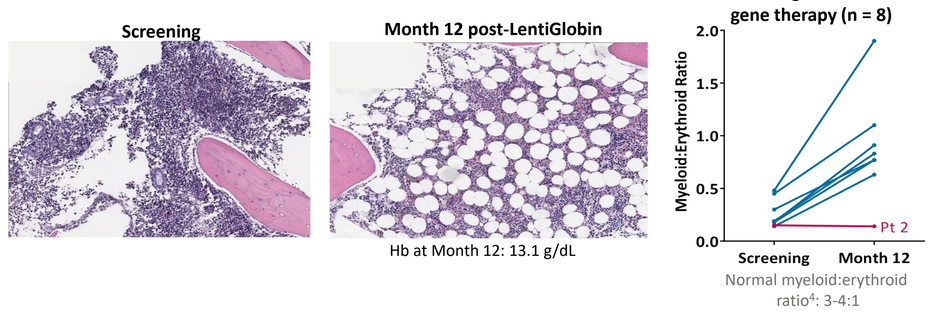


Table 3. HGB-204 and HGB-207: Safety profile of LentiGlobin in patients with non-β^0/β^0 genotypes

Non-hematologic* grade ≥3 AEs in ≥2 patients in HGB-207† LentiGlobin infusion to up to 2 years of follow-up	HGB-204 N = 10 n (%)	HGB-207 N = 20 n (%)
Stomatitis	8 (80)	12 (60)
Febrile neutropenia	6 (60)	6 (30)
Pyrexia	–	4 (20)
Epistaxis	–	3 (15)
Veno-occlusive liver disease	1 (10)	3 (15)
ALT increased	–	2 (10)
Bilirubin increased	–	2 (10)
Hypoxia	–	2 (10)
Neutropenic sepsis	–	2 (10)
Pharyngeal inflammation	2 (20)	2 (10)

*Hematologic AEs commonly observed post-transplant have been excluded. †In HGB-204, non-hematologic grade ≥3 AEs also included 3/10 (30%) patients with irregular menstruation.
AE, adverse event; ALT, alanine aminotransferase; VOD, veno-occlusive liver disease.

- **One grade ≥3 AE was considered possibly related to LentiGlobin**
  - Grade 3 thrombocytopenia in HGB-207
- **No vector-mediated replication-competent lentivirus**
- **No evidence of clonal dominance**
- **No deaths or graft failure**
- **Serious adverse events in ≥ 2 patients regardless of genotype**
  - 204: VODs (n=2), thrombosis (n=2)
  - 207: VODs (n=3), pyrexia (n=2), and thrombocytopenia (n=2)
- **Serious veno-occlusive liver disease**
  - HGB-204: 2 grade 3 serious VODs
  - HGB-207: 3 grade 4 serious VODs
  - All events resolved following defibrotide

SUMMARY

Northstar (HGB-204):
- Patients with TDT have been followed for up to 4.5 years after LentiGlobin gene therapy
- 80% (8/10) of patients with non-β^0/β^0 genotypes achieved durable transfusion independence (TI)
  - Total Hb was 9.1 – 14.1 g/dL at last visit; HbA^{T87Q} remains stable
  - RBC indices were generally within normal ranges
  - LIC decreased over time in patients who achieved TI

Northstar-2 (HGB-207):
- 4/5 evaluable patients with non-β^0/β^0 genotypes achieved transfusion independence.
  - Weighted average Hb during TI of 12.4 g/dL
- 13/14 patients with ≥3 months follow-up after LentiGlobin gene therapy are transfusion free
- HbA^{T87Q} stabilized approximately 6 months after LentiGlobin infusion in patients who stopped transfusions
- Bone marrow histology and myeloid to erythroid ratio showed improvements in erythropoiesis in patients who stopped transfusions

Safety profile:
- The safety profile of LentiGlobin is generally consistent with busulfan myeloablative conditioning
- Delayed platelet engraftment was observed, but there were no serious bleeding events after infusion

ACKNOWLEDGEMENTS

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DISCLOSURES

Dr. Hongeng has nothing to disclose.

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