Long-term safety and efficacy of LentiGlobin gene therapy in patients with transfusion-dependent β-thalassemia following completion of the phase 1/2 Northstar study

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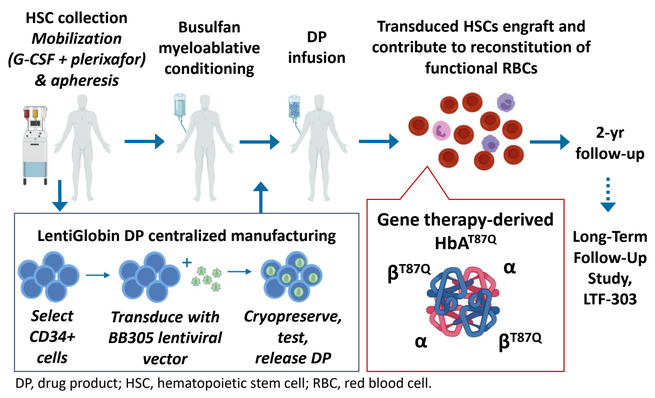
BACKGROUND

- Transfusion-dependent β-thalassemia (TDT) is a severe genetic disease treated by 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 transplantation is associated with risks of transplant-related mortality and GVHD.
- Patients with TDT may benefit from gene therapy involving the addition of the β-globin gene to HSCs ex vivo, to produce functional hemoglobin (Hb).
- LentiGlobin gene therapy is an investigational treatment that contains autologous CD34+ cells transduced *ex vivo* with the BB305 lentiviral vector encoding β-globin with a T87Q substitution enabling production of functional adult Hb.
- Northstar (HGB-204) is an international, multi-center, Phase 1/2, open-label, single-arm study of LentiGlobin gene therapy in adolescents/adults with TDT.[3]

METHODS

- Patients aged 12 to 35 years with TDT (≥ 100 mL/kg/year of red blood cells [RBCs] or ≥ 8 RBC transfusions/year) were enrolled in the study.
- Autologous CD34+ cells were mobilized using G-CSF and plerixafor and were transduced with the BB305 lentiviral vector.
- Patients underwent myeloablative conditioning with single-agent busulfan followed by LentiGlobin infusion.
- Patients were monitored for safety and efficacy for 2 years and were offered participation in the long-term follow-up study, LTF-303.
- Primary endpoints in HGB-204:
  - Sustained production of ≥ 2 g/dL of HbA^{T87Q} 18 – 24 months post-infusion
  - Transfusion independence (TI) (weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months)
- Data is presented as of 14 September 2018

Figure 1. Northstar study design



DP, drug product; HSC, hematopoietic stem cell; RBC, red blood cell.

STUDY STATUS

Figure 2. Patient disposition

Consented
N=19

Inadequate mobilization N=1

Stem Cell Mobilization Complete
N=18

LentiGlobin Infused
N=18

Median follow-up: 38.9 months
(min – max: 29.3 – 48.1 months)

All patients have enrolled in the long-term follow-up study, LTF-303

RESULTS

Table 1. Patient baseline characteristics

Patient Characteristics		N = 18
Genotypes	Non-β^0/β^0	**10**
	β^0/β^0	**8**
Age at consent median (min – max), yrs		**20** (12 – 35)
Pre-study RBC transfusion volume annualized median (min – max), mL/kg/yr		**169** (124 – 273)
Liver iron concentration (LIC) median (min – max), mg Fe/g dw		**5.7** (0.4 – 26.4)
LIC < 7 mg/g, n, %		**10** (56)
LIC ≥ 7 – < 15 mg/g, n, %		**6** (33)
LIC ≥ 15 mg/g n, %		**2** (11)
Cardiac T2* median (min – max), msec		**35** (10 – 54)
Serum ferritin† median (min – max), pmol/L		**3147** (748 – 8629)

†N=17, baseline serum ferritin was not available for one patient. RBC, red blood cell.

Table 2. Treatment characteristics

Mobilization/Apheresis Characteristics	N = 18 median (min – max)
Apheresis procedures per mobilization, n	**2** (1 – 3)
Mobilization cycles per patient, n	**1** (78%) **2** (22%)
Conditioning Characteristics	
Avg daily busulfan AUC, μM*min	**4093** (3030 – 4714)
Drug Product Characteristics	
Cell dose, x10^6 CD34+ cells/kg	**8.1** (5.2 – 18.1)
Vector copy number,† vector copies/diploid genome	**0.7** (0.3 – 1.5)
CD34+ cells transduced,† %	**31.5** (17 – 58)

†22 drug product lots manufactured for 18 patients. AUC, area under the curve.

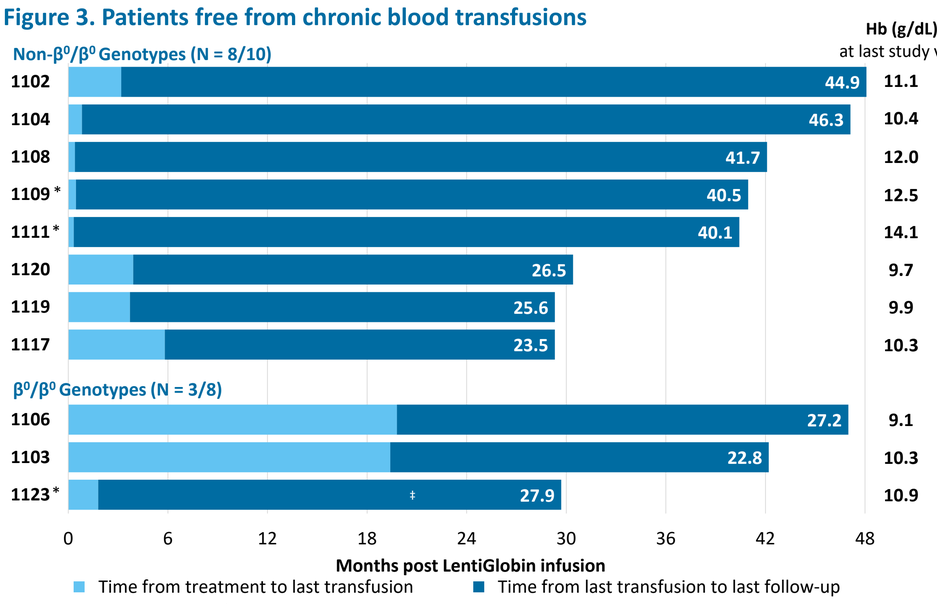
Table 3. Neutrophil and platelet engraftment

Engraftment	N=18 median (min – max)
Neutrophil engraftment, ANC ≥ 500 cells/μL x 3 days, day	**18.5** (14 – 30)
Platelet engraftment, Platelets ≥ 20k/μL, day	**39.5** (19 – 191)

ANC, absolute neutrophil count.

- Delayed platelet engraftment was observed in some patients
- Small patient numbers and potential overlapping contributing factors limit the ability to associate platelet engraftment time with a causal factor

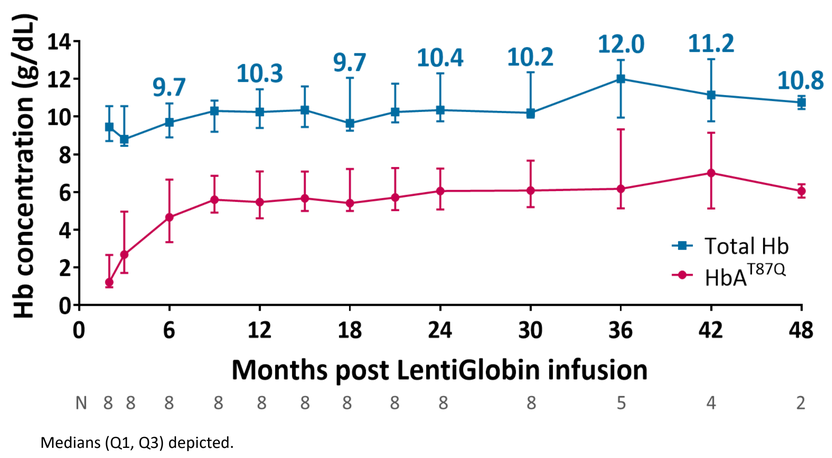
Figure 3. Patients free from chronic blood transfusions



*Indicates male patients; ‡Patient had a single transfusion for an acute event of cat scratch disease.

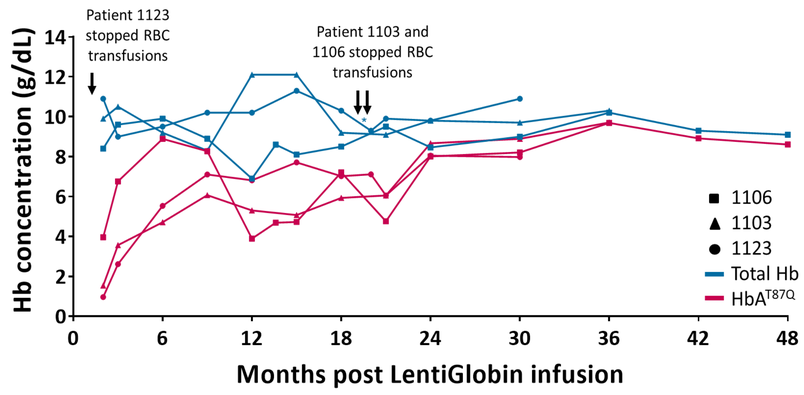
- 89% (16/18) patients achieved the primary endpoint of ≥ 2 g/dL of HbA^{T87Q} between Months 18 – 24
- 80% (8/10) patients with non-β^0/β^0 genotypes achieved and maintained transfusion independence
- 1/8 patients with β^0/β^0 genotypes achieved transfusion independence during HGB-204
  - 2/8 patients with β^0/β^0 genotypes achieved transfusion independence after completion of HGB-204 in the long-term follow-up study, LTF-303

Figure 4. Median hemoglobin in patients with non-β^0/β^0 genotypes who achieved transfusion independence



Medians (Q1, Q3) depicted.

Figure 5. Hemoglobin in patients with β^0/β^0 genotypes who achieved transfusion independence



*Patient 1123 had a single transfusion for an acute event of cat scratch disease.

Table 4. Safety profile following LentiGlobin infusion

Non-hematologic* grade ≥ 3 AEs reported in ≥ 2 patients *DP infusion to 2 years follow-up*	LIC < 7 mg/g n = 10 n (%)	LIC ≥ 7 mg/g n = 8 n (%)	Busulfan AUC < 4000 n = 6 n (%)	Busulfan AUC ≥ 4000 n = 12 n (%)	All patients N=18 n (%)
Stomatitis	8 (80)	4 (50)	5 (83)	7 (58)	12 (67)
Febrile neutropenia	5 (50)	5 (63)	2 (33)	8 (67)	10 (56)
Pharyngeal inflammation	2 (20)	3 (38)	0 (0)	5 (42)	5 (28)
Menstruation irregular	3 (30)	0 (0)	2 (33)	1 (8)	3 (17)
Epistaxis	0 (0)	2 (25)	1 (17)	1 (8)	2 (11)
Veno-occlusive liver disease	0 (0)	2 (25)	0 (0)	2 (17)	2 (11)
Serious AEs* reported in ≥ 2 patients *DP infusion to last follow-up*					
Thrombosis§	1 (10)	1 (13)	1 (17)	1 (8)	2 (11)
Veno-occlusive liver disease	0 (0)	2 (25)	0 (0)	2 (17)	2 (11)

AE, adverse event; DP, drug product; LIC, liver iron concentration.
*Hematologic AEs commonly observed post-transplant have been excluded; §Included 1 vena cava thrombosis and 1 intracardiac thrombus.

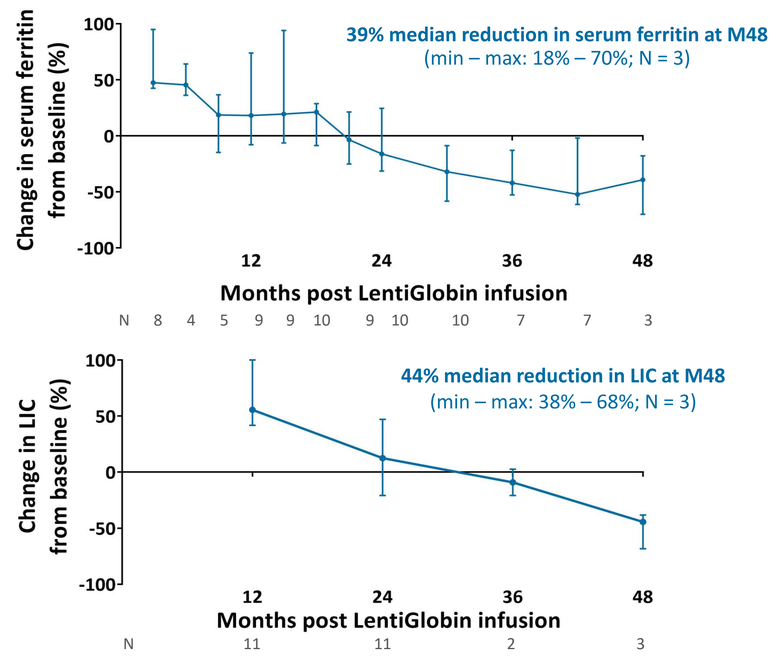
- Due to the small population size, no clear effect of baseline LIC and busulfan AUC on the occurrence of AEs can be determined
- No grade ≥ 3 DP-related AEs
- No deaths or graft failure
- No vector-mediated replication competent lentivirus
- Two grade 3, serious episodes of VOD were reported; both resolved after defibrotide treatment

Table 5. Incidence of liver veno-occlusive disease

		Pt 1113	Pt 1121	No VOD (N = 16) median (min – max)
Age (yrs) and Gender		20 F	16 F	20.5 (12 – 35); 68.8% Female
VOD prophylaxis		None	None	37.5% (6/16)
Screening	**Imaging LIC**, mg Fe/g dw	8.4	10.4	4.9 (0.4 – 26.4)
	AST, U/L	55	29	27 (9 – 74)
	ALT, U/L	121	26	21 (6 – 85)
	Total bilirubin, μmol/L	20.5	71.8	33.2 (12.0 – 104.3)
Busulfan dosing schedule		Q 24 hrs	Q 24 hrs	Q 24 hrs
Average busulfan AUC,‡ μM*min		4374	4025	4092.5† (3030 – 4714)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; VOD, liver veno-occlusive disease; Pt, patient.
†Estimated average daily busulfan exposure over 4 days. Target busulfan AUC of 1000 (min – max 900 – 1200) μM*min for every 6 hours dosing, or 4000 (min – max 3600 – 5000) μM*min for once daily dosing.

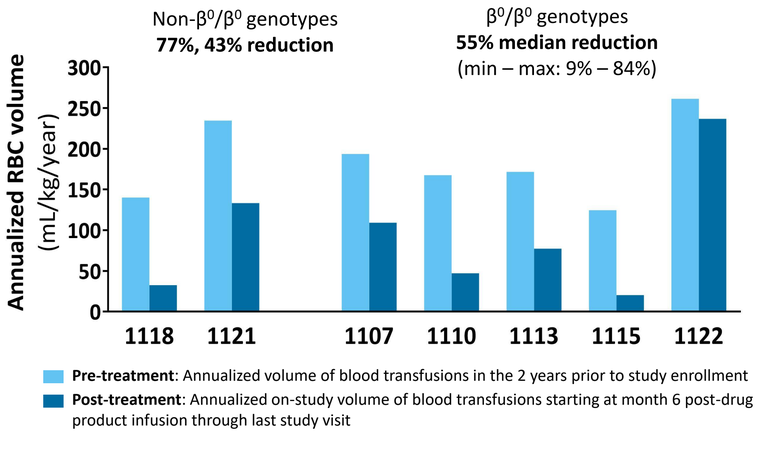
Figure 6. Percent change in serum ferritin and liver iron concentration from baseline in patients who achieved transfusion independence



Medians (Q1, Q3) depicted. One patient did not have a baseline serum ferritin level. LIC, liver iron concentration

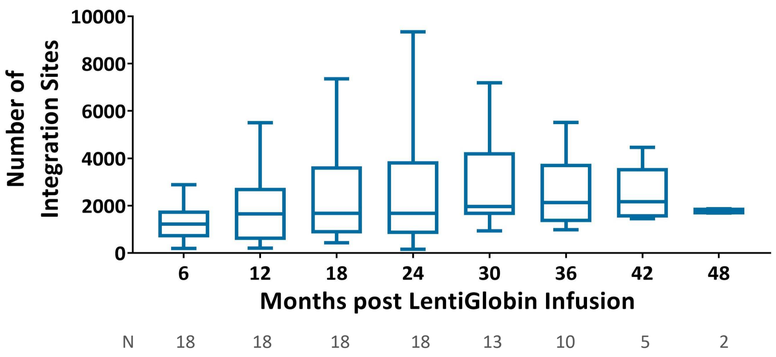
- Patients re-initiated iron chelation therapy a median of 13 months after LentiGlobin infusion (min – max: 2 – 16 months)

Figure 7. Reduction in blood transfusion volume in patients still receiving transfusions



Pre-treatment: Annualized volume of blood transfusions in the 2 years prior to study enrollment
Post-treatment: Annualized on-study volume of blood transfusions starting at month 6 post-drug product infusion through last study visit

Figure 8. Integration site analysis over time



- Polyclonal vector integration profile is maintained over time
- No clonal dominance has been observed

SUMMARY

- **89% (16/18) of patients achieved ≥ 2 g/dL of HbA^{T87Q} between Months 18 – 24**
- **80% (8/10) of patients with non-β^0/β^0 genotypes achieved TI during HGB-204**
  - **With a median follow-up of 39 months in all patients, 100% of patients with non-β^0/β^0 genotypes have maintained TI**
- **38% (3/8) of patients with β^0/β^0 genotypes achieved TI during HGB-204 or LTF-303**
- **Reduced iron burden was observed in patients achieving TI in the setting of iron chelation**
- **The safety profile of LentiGlobin is consistent with myeloablative conditioning including events of VOD**
  - **Some patients experienced delayed platelet engraftment**
- **Two ongoing Phase 3 studies, Northstar-2 and Northstar-3, are evaluating refined manufacturing of LentiGlobin with the goal to improve patient outcomes**

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DISCLOSURE

Dr. Hongeng has nothing to disclose.

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1. Cao, et al. *Genetics in Medicine.* 2010;12(2):61-76.
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