LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassemia: Outcomes from the Phase 1/2 Northstar and Phase 3 Northstar-2 Studies

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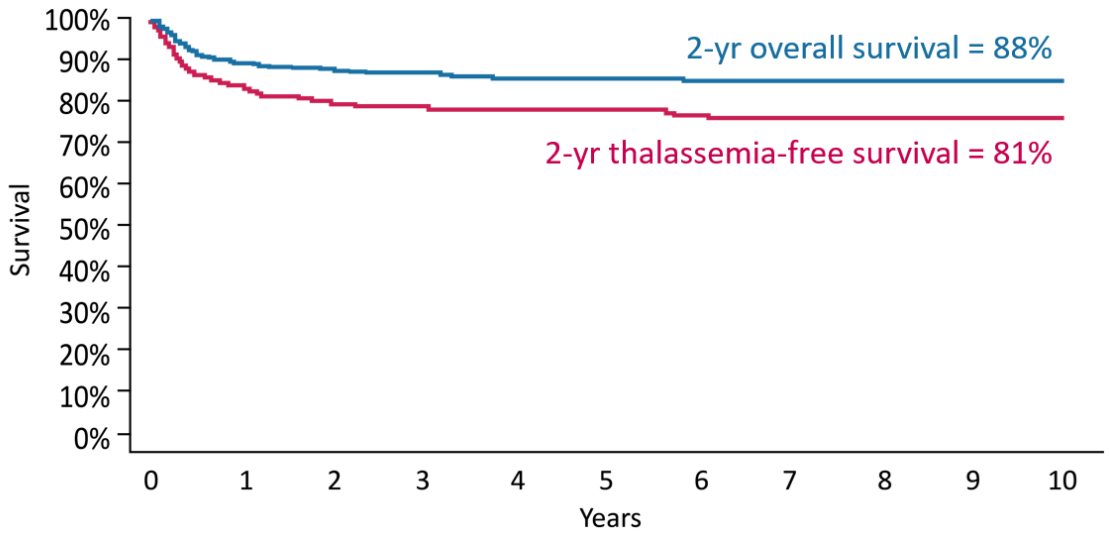
LentiGlobin for transfusion-dependent β-thalassemia (TDT)

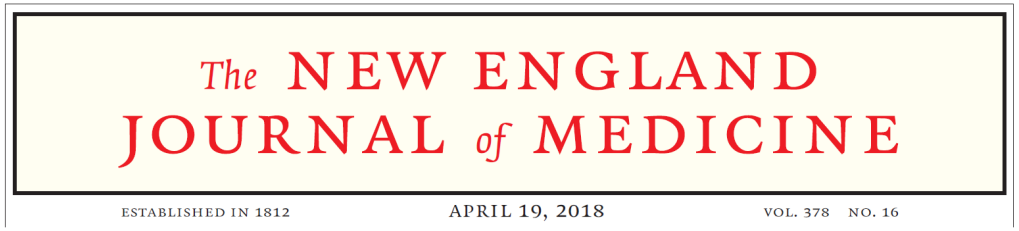
The wider application of allo-HSCT for transfusion-dependent β-thalassemia is limited by donor availability and risks of GVHD/TRM

Survival following allo-HSCT in patients with β-thalassemia (N = 1493)



Baronciani et al. Bone Marrow Transplant 2016; 51:536-41.

LentiGlobin gene therapy by autologous CD34+ HSCs transduced with BB305 lentiviral vector overcomes limitations of donor availability and GVHD



Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

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Thompson et al. N Engl J Med. 2018;378(16):1479-1493.

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; GVHD, graft vs host disease; HSC, hematopoietic stem cell; TRM, treatment-related mortality.

Northstar (HGB-204) and Northstar-2 (HGB-207): Study status

HGB-204

non-β^0/β^0 and β^0/β^0 genotypes

Completed

Phase 1/2, international, open-label, single-arm study

Primary Efficacy Endpoints

- **≥ 2 g/dL HbA^{T87Q} 18 – 24 months post-infusion**
- **RBC Transfusion Independence**

All 18 patients infused

Median follow-up: 38.9 months

(min – max: 29.3 – 48.1 months)

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

HGB-207

non-β^0/β^0 genotypes

Ongoing

Phase 3, international, open-label, single-arm study

Primary Endpoint

RBC Transfusion Independence

Weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months

16 patients infused

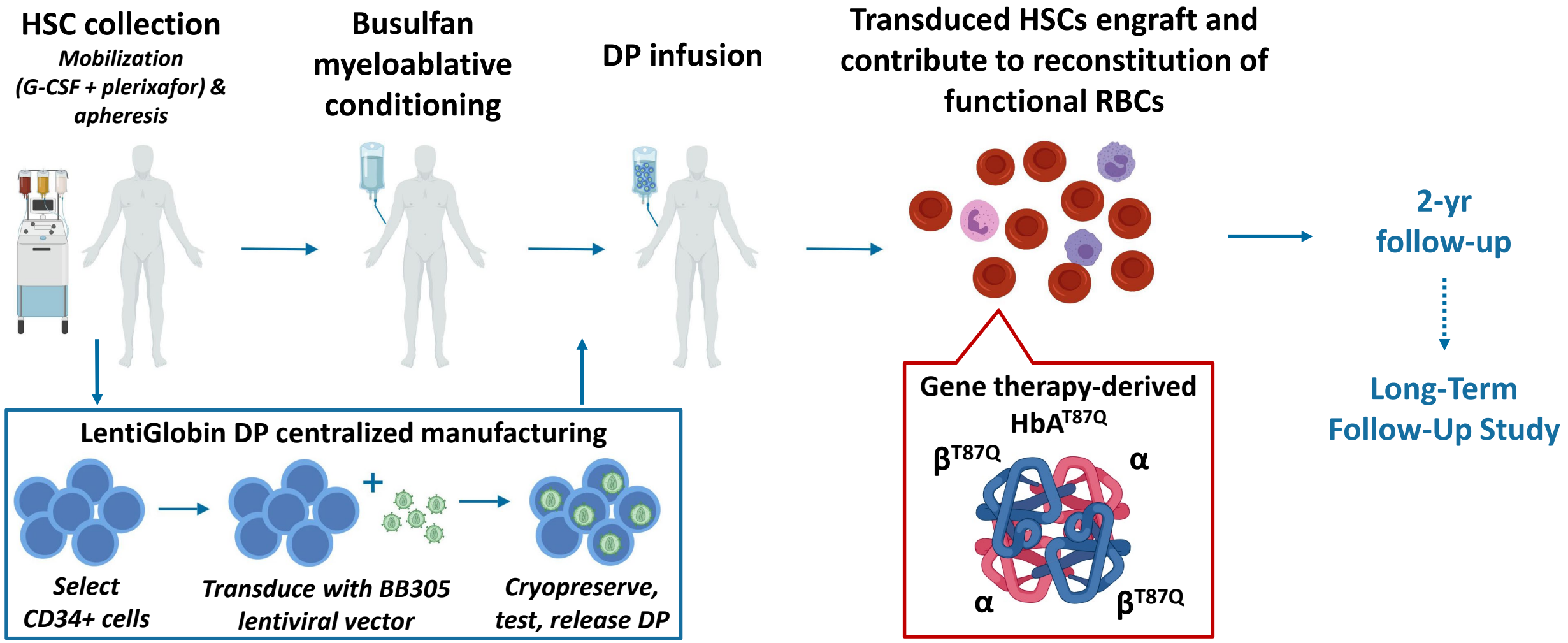
Target enrollment: 23 patients

Median follow-up: 9.3 months

(min – max: 0.7 – 20.4 months)

Hb, hemoglobin; RBC, red blood cell.

HGB-204 and HGB-207: Study design



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

HGB-204 and HGB-207: Patient, drug product, treatment characteristics

	HGB-204 (N = 18)	HGB-207 (N = 16)
Patient Characteristics		
Genotypes	**8** β^0/β^0 **6** β^E/β^0 **4** Other	**7** β^+/β^0 **6** β^E/β^0 **3** β^+/β^+
Age at consent median (min – max), yrs	**20** (12 – 35)	**19** (8 – 34)
Pre-study RBC transfusion volume annualized median (min – max), mL/kg/yr	**169** (124 – 273)	**192** (152 – 274)
Liver iron concentration median (min – max), mg/g	**5.7** (0.4 – 26.4)	**6.4** (1.0 – 41.0)
Splenectomy n, %	**6** (33)	**4** (25)

	HGB-204 (N = 18) median (min – max)	HGB-207 (N = 16) median (min – max)
Drug Product Characteristics		
Cell dose CD34+ cells x10^6/kg	**8.1** (5.2 – 18.1)	**7.7** (5.0 – 19.4)
VCN[†] vector copies/diploid genome	**0.7** (0.3 – 1.5)	**3.1** (2.1 – 5.6)
% CD34+ cells transduced[‡]	**31.5** (17 – 58)	**82** (53 – 90)
Treatment Characteristics		
Avg daily busulfan AUC µM*min	**4093** (3030 – 4714)	**4545** (3709 – 8947)
Neutrophil engraftment[^] ANC ≥ 500 cells/µl x 3 days, days	**18.5** (14 – 30)	**19** (13 – 32)
Platelet engraftment[^] Platelets >20k/µl, days	**39.5** (19 – 191)	**44.5** (20 – 84)

[†]HGB-204: 22 DP lots for 18 patients; HGB-207: 20 DP lots for 16 patients; [‡]HGB-207: 19 DP lots for 15 patients, one %LVV+ was not available at time of datacut; [^]HGB-207: As of the datacut, 1 patient (1-month follow-up) and 4 patients (≤2 months follow-up) had not achieved neutrophil and platelet engraftment, respectively. ANC, absolute neutrophil count; DP, drug product; RBC, red blood cell.

HGB-204 and HGB-207: Platelet engraftment following LentiGlobin infusion

Platelet engraftment by patient or treatment characteristic†

	Day of platelet engraftment median (min – max)
Splenectomy status	
No splenectomy, n=21	**46** (20 – 191)
Splenectomy, n=9	**36** (19 – 53)
G-CSF administered between Days 1-21	
Received G-CSF,‡ n=10	**47.5** (31 – 191)
No G-CSF, n=20	**41.5** (19 – 84)
Drug product cell dose	
< Median of 8.1 CD34+ cells x10^6/kg, n=15	**44** (30 – 191)
≥ Median of 8.1 CD34+ cells x10^6/kg, n=15	**36** (19 – 66)
Busulfan AUC	
< Median of 4206 µM*min, n=15	**38** (20 – 191)
≥ Median of 4206 µM*min, n=15	**44** (19 – 91)

- 68% (23/34) had any grade bleeding AEs from DP infusion through 2 years post-infusion
  - Grade ≥ 3 bleeding AEs DP infusion to plt engraftment:
    - Epistaxis (n=5, Gr 3)
    - Gingival bleeding (n=1, Gr 3)
  - One serious AE of hypotension due to prolonged severe epistaxis before plt engraftment
- Patient number and potential overlapping contributing factors limit ability to associate with a causal factor

†Analysis includes patients who achieved platelet engraftment in HGB-204 or HGB-207; ‡In HGB-207, G-CSF was not recommended to be used prior to Day 21, however 3 patients received G-CSF within this timeframe.
AE, adverse event; AUC, area under the curve; DP, drug product; G-CSF, granulocyte-colony stimulating factor; plt, platelet.

HGB-204 and HGB-207: Safety profile is generally consistent with myeloablative conditioning

HGB-204 (N=18)

Non-hematologic* grade ≥ 3 AEs in ≥ 2 patients DP infusion to up to 2 years of follow-up	n (%)
Stomatitis	12 (67)
Febrile neutropenia	10 (56)
Pharyngeal inflammation	5 (28)
Irregular menstruation	3 (17)
Epistaxis	2 (11)
Veno-occlusive liver disease	2 (11)
Serious AEs* in ≥ 2 patients DP infusion to last follow-up	
Thrombosis†	2 (11)
Veno-occlusive liver disease	2 (11)

HGB-207 (N=16)

Non-hematologic* grade ≥ 3 AEs in ≥ 2 patients DP infusion to last follow-up	n (%)
Stomatitis	9 (56)
Febrile neutropenia	4 (25)
Epistaxis	3 (19)
Pyrexia	3 (19)
Veno-occlusive liver disease	3 (19)
ALT increased	2 (13)
Bilirubin increased	2 (13)
Hypoxia	2 (13)
Pharyngeal inflammation	2 (13)
Serious AEs* in ≥ 2 patients DP infusion to last follow-up	
Veno-occlusive liver disease	3 (19)

DP-related AEs: Grade 1 events of abdominal pain (n=2), dyspnea (n=1), dysplasia (n=1), hot flush (n=1), non-cardiac chest pain (n=1), pain in extremity (n=1), and Grade 3 thrombocytopenia (n=1)

No deaths, graft failure, vector-mediated RCL, or clonal dominance

*Hematologic AEs observed post-transplant have been excluded; †Included 1 vena cava thrombosis and 1 intracardiac thrombus. AE, adverse event; DP, drug product; RCL, replication competent lentivirus.

HGB-204 and HGB-207: Veno-occlusive liver disease

- 5 serious episodes of VOD were reported; all resolved after defibrotide treatment

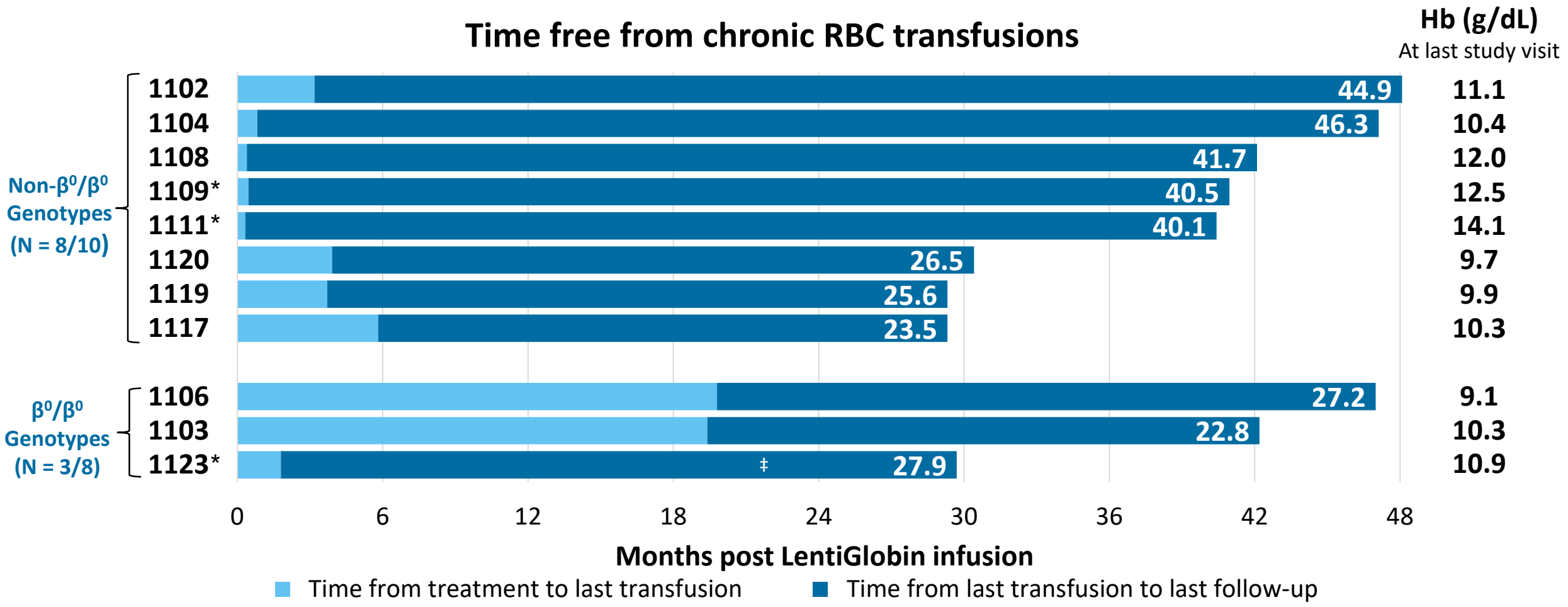
		VOD (N=5)					No VOD (N = 29) median (min – max)
		HGB-204		HGB-207			
		1113	1121	Pt 9	Pt 10	Pt 12	
Event grade		Gr 3	Gr 3	Gr 4	Gr 4	Gr 4	–
Age (yrs) and Gender		20 F	16 F	12 M	12 F	34 M	20 (8 – 35); 62% Female
VOD prophylaxis		None	None	None	None	Ursodeoxycholic acid Day -8 to +38	48% (14/29)
Screening	**Imaging LIC**, mg Fe/g dw	8.4	10.4	1.0	5.6	8.5	5 (0.4 – 41)
	AST, U/L	55	29	23	14	40	23 (9 – 74)
	ALT, U/L	121	26	32	7	43	22 (6 – 164)
	Total bilirubin, µmol/L	20.5	71.8	20.9	22.9	25.3	34.0 (12.0 – 104.3)
Busulfan dosing schedule		Q 24 hrs	Q 24 hrs	Q 24 hrs	Q 24 hrs	Q 24 hrs	82% (23/28[†]) Q 24 hrs 18% (5/28[†]) Q 6 hrs
Average busulfan AUC,[‡] µM*min		4374	4025	4595	4471	4788	4205[†] (3030 – 8947)

[†]N = 28, conditioning regimen not available for one patient as of the datacut; [‡]Estimated average daily busulfan exposure over 4 days.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; Gr, grade; LIC, liver iron content; Pt, patient; VOD, veno-occlusive liver disease.

HGB-204: Achievement of transfusion independence

8/10 patients with non-β^0/β^0 genotypes; 3/8 patients with β^0/β^0 genotypes^

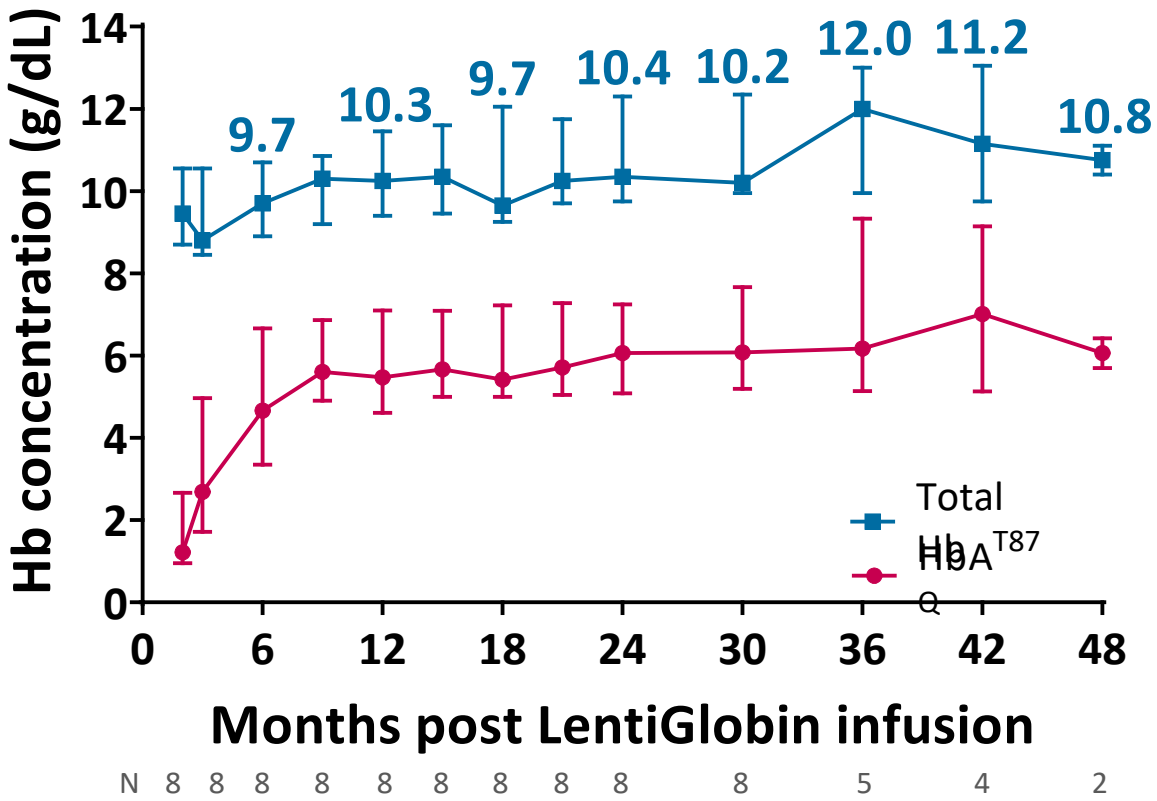


89% (16/18) patients achieved the primary endpoint of ≥2 g/dL of HbA^{T87Q} between Months 18 – 24

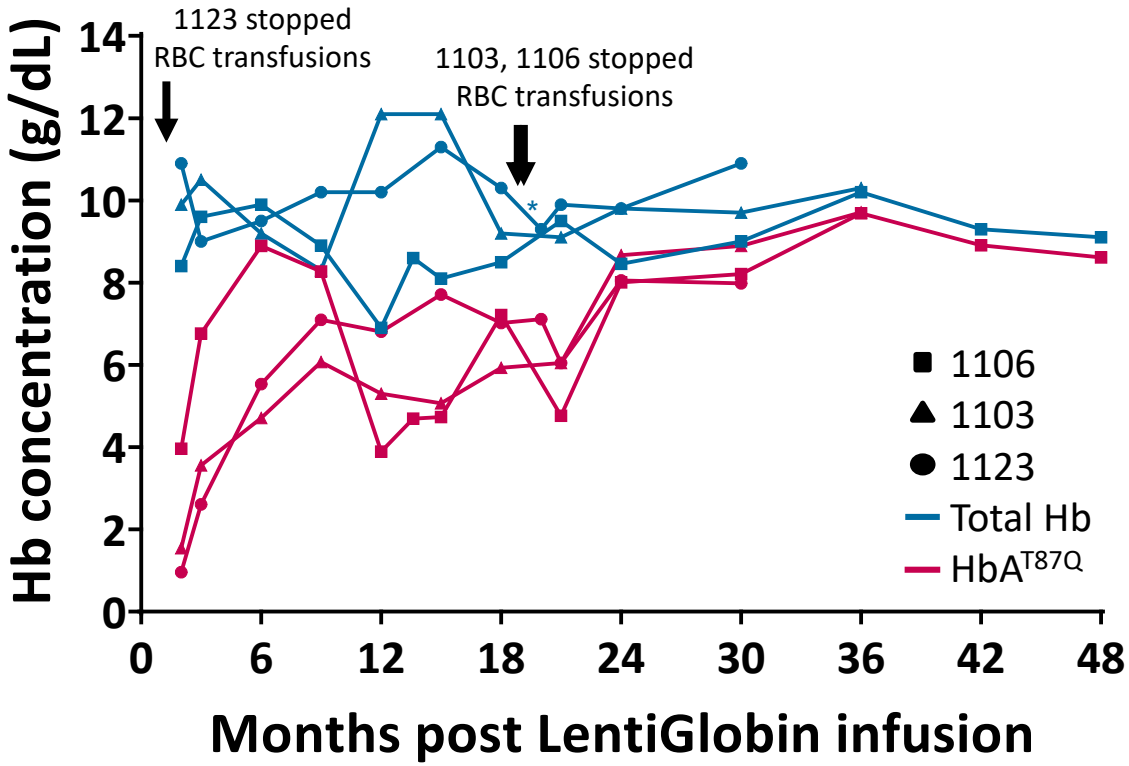
^At any time in HGB-204 or LTF-303; *Indicates male patients; ‡Patient had a single transfusion for an acute event of cat scratch disease.
Transfusion independence (weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months). Hb, hemoglobin. RBC, red blood cell.

HGB-204: HbA^{T87Q} is stable in patients who achieved transfusion independence

Patients with non-β^0/β^0 genotypes



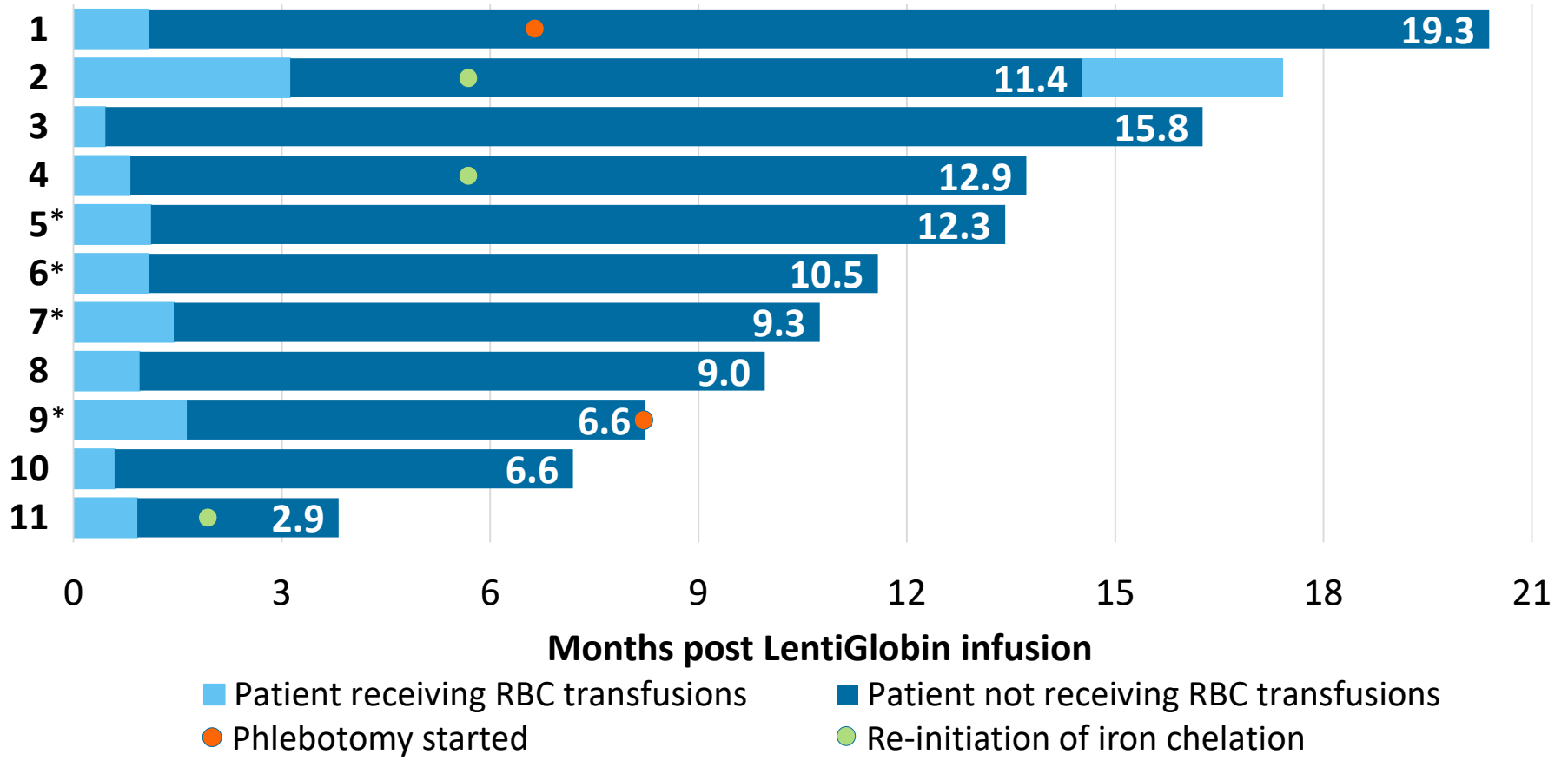
Patients with β^0/β^0 genotypes



Medians (Q1, Q3) depicted for non-β^0/β^0 genotypes; *Patient 1123 had a single transfusion for an acute event of cat scratch disease. Hb, hemoglobin.

HGB-207: 10/11 patients are transfusion free with Hb > 11 g/dL

Time free from chronic RBC transfusions in patients with ≥ 3 months follow-up



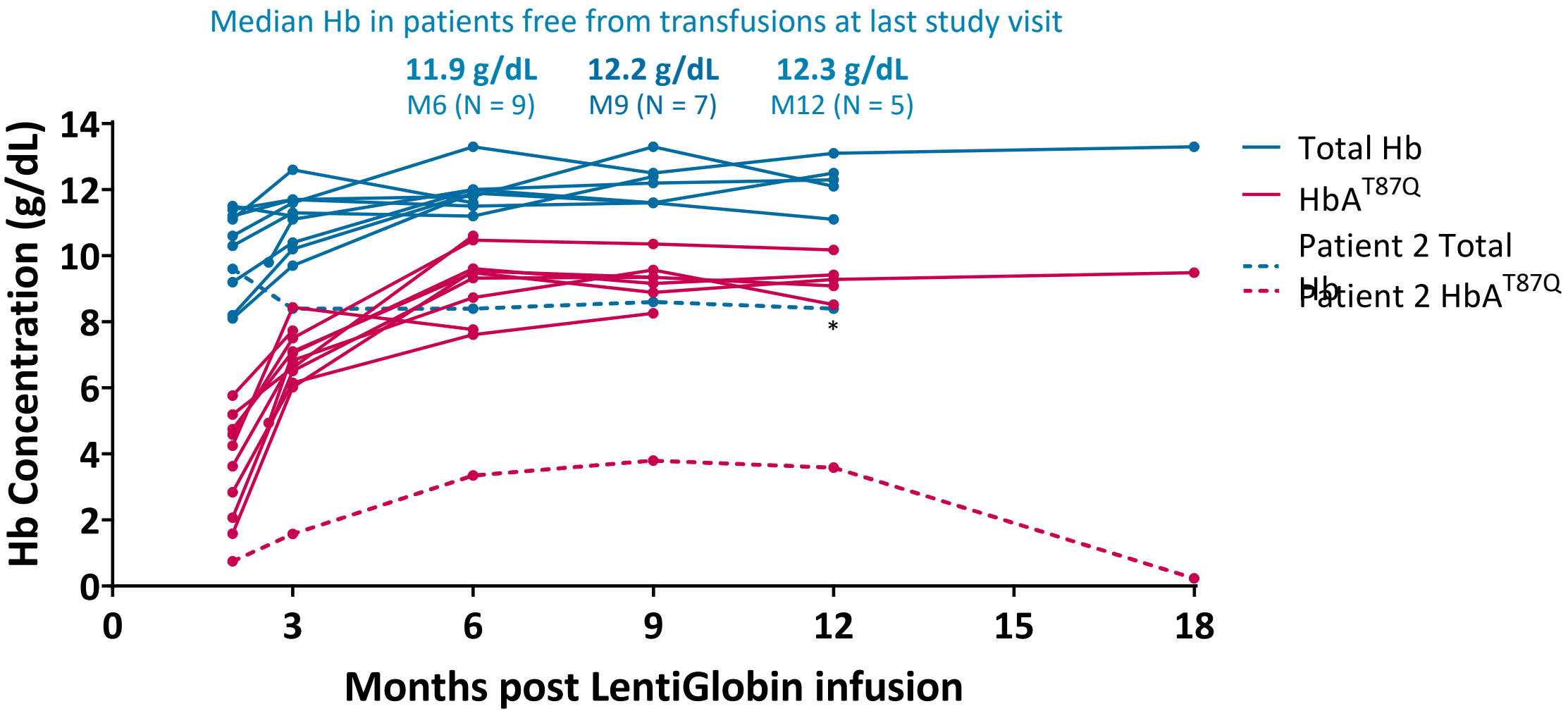
Patients 1 and 3 have achieved the protocol definition of transfusion independence

(Weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months)

*Male patients; ‡Hb supported by transfusions; Hb, hemoglobin; RBC, red blood cell.

Data as of September 14, 2018

HGB-207: Stable transfusion-free total Hb and gene therapy-derived HbA^{T87Q}



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

Summary of LentiGlobin in patients with transfusion-dependent β-thalassemia

HGB-204 – Up to 4 years follow-up

- 80% (8/10) patients with TDT and non-β^0/β^0 genotypes have achieved durable transfusion independence
- 38% (3/8) patients with TDT and β^0/β^0 genotypes have achieved transfusion independence

HGB-207 – Up to 20 months follow-up

- Manufacturing refinements have translated into robust and stable total Hb levels
- 10/11 adults and adolescents with TDT and non-β^0/β^0 genotypes with ≥ 3 months follow-up have stopped RBC transfusions
- 2/3 evaluable patients have achieved transfusion independence

Safety

- Safety profile remains generally consistent with myeloablative busulfan conditioning, including veno-occlusive liver disease
- All patients with > 2 months follow-up have engrafted; some patients had delayed platelet engraftment
  - Data set does not permit identification of causal factors due to patient number and potential overlapping risk
- No deaths, graft failure, vector-mediated RCL, or clonal dominance

AE, adverse event; Hb, hemoglobin; RBC, red blood cell; RCL, replication competent lentivirus; TI, transfusion independence; TDT, transfusion-dependent β-thalassemia

Thank you to the study participants and their families

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Children's Hospital of Philadelphia, Philadelphia, USA

UCSF Benioff Children's Hospital, Oakland, USA

University of California, Los Angeles, Los Angeles, USA

University College London Hospital, London, UK

UCL Great Ormond Street Hospital, London, UK

Hôpital de la Timone & Institut Paoli-Calmettes, Marseille, France

IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

Medizinische Hochschule Hannover, Hannover, Germany

Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Royal Prince Alfred Hospital, Sydney Medical School, University of Sydney, Camperdown, Australia

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- Sarah Hunter
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- Jun Yu
- Srujana Sarikonda
- Kimberly Price