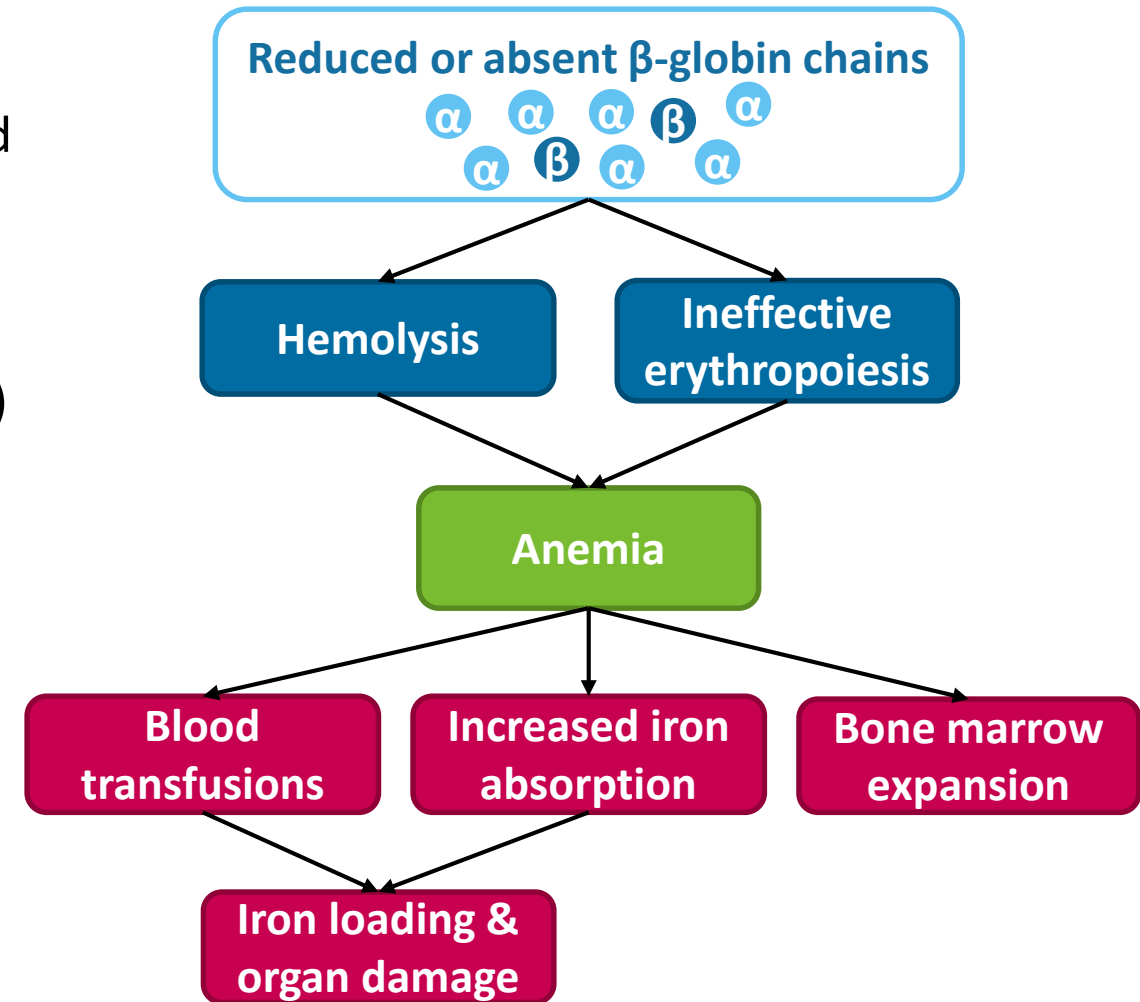


Updated results from the ongoing Northstar-2 (HGB-207) trial of LentiGlobin gene therapy in patients with transfusion-dependent β -thalassemia and non- β^0/β^0 genotypes

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β -thalassemia is characterized by reduced or absent production of functional β -globin

- Endemic in South Asia, the Middle East, North Africa, and Southern Europe¹⁻³
 - Migration is changing the global distribution of the disease
- Patients with transfusion-dependent β -thalassemia (TDT) require lifelong blood transfusions to enable survival¹⁻³
 - Iron overload
 - Organ damage
- Allo-HSCT is potentially curative but is associated with transplant-related risk and donor limitations¹



Allo-HSCT, allogeneic hematopoietic stem cell transplantation

1. Galanello et al. *Orphanet J Rare Dis.* 2010;5:11. 2. Cappellini, et al. 3rd ed. *Thalassaemia International Federation*; 2014. 3 Colah, et al. *Expert Rev Hematol.* 2010;3(1):103-117.

Northstar-2 (HGB-207): Phase 3 study in patients with TDT and non- β^0/β^0 genotypes



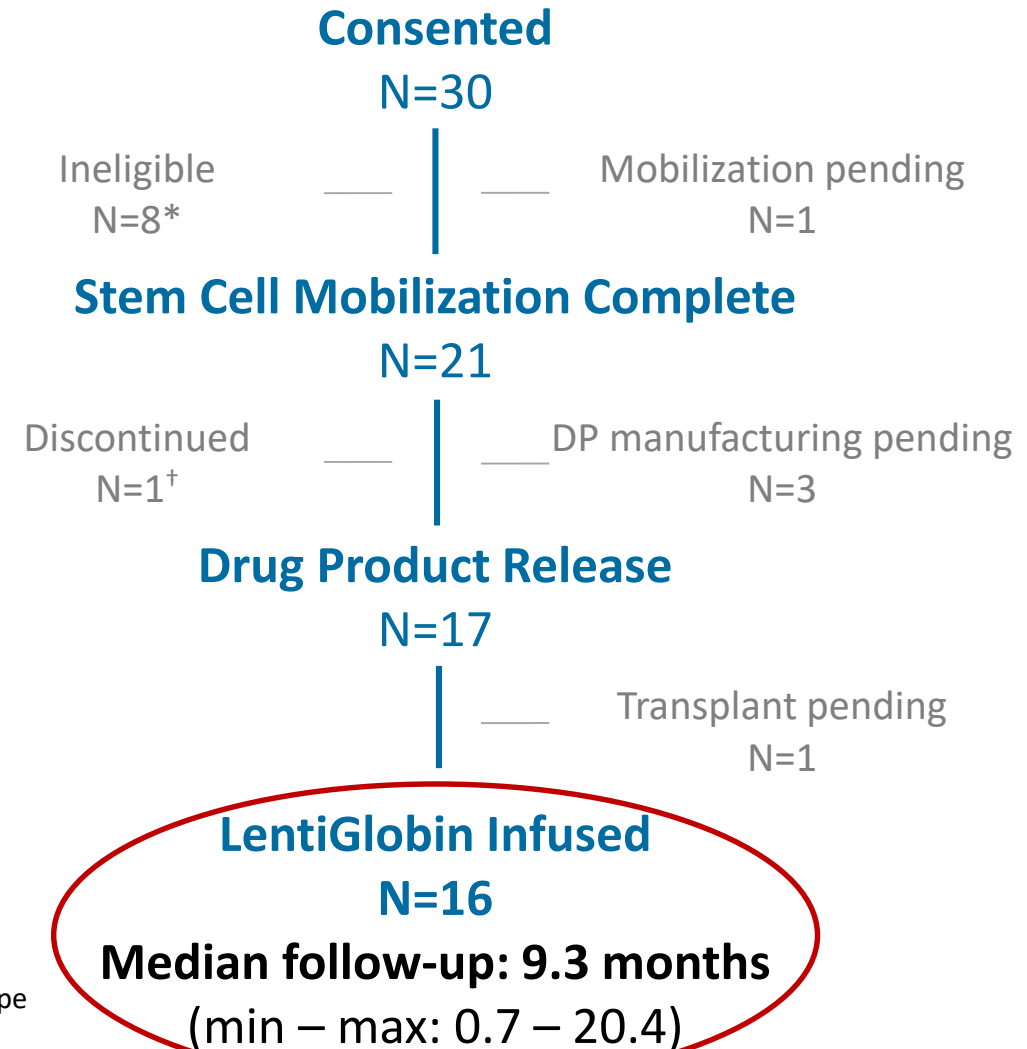
HGB-207

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

Target enrollment: **23 patients \leq 50 years of age
with TDT and non- β^0/β^0 genotypes**

Primary endpoint: Transfusion Independence

Weighted average Hb \geq 9 g/dL without any
transfusions for \geq 12 months

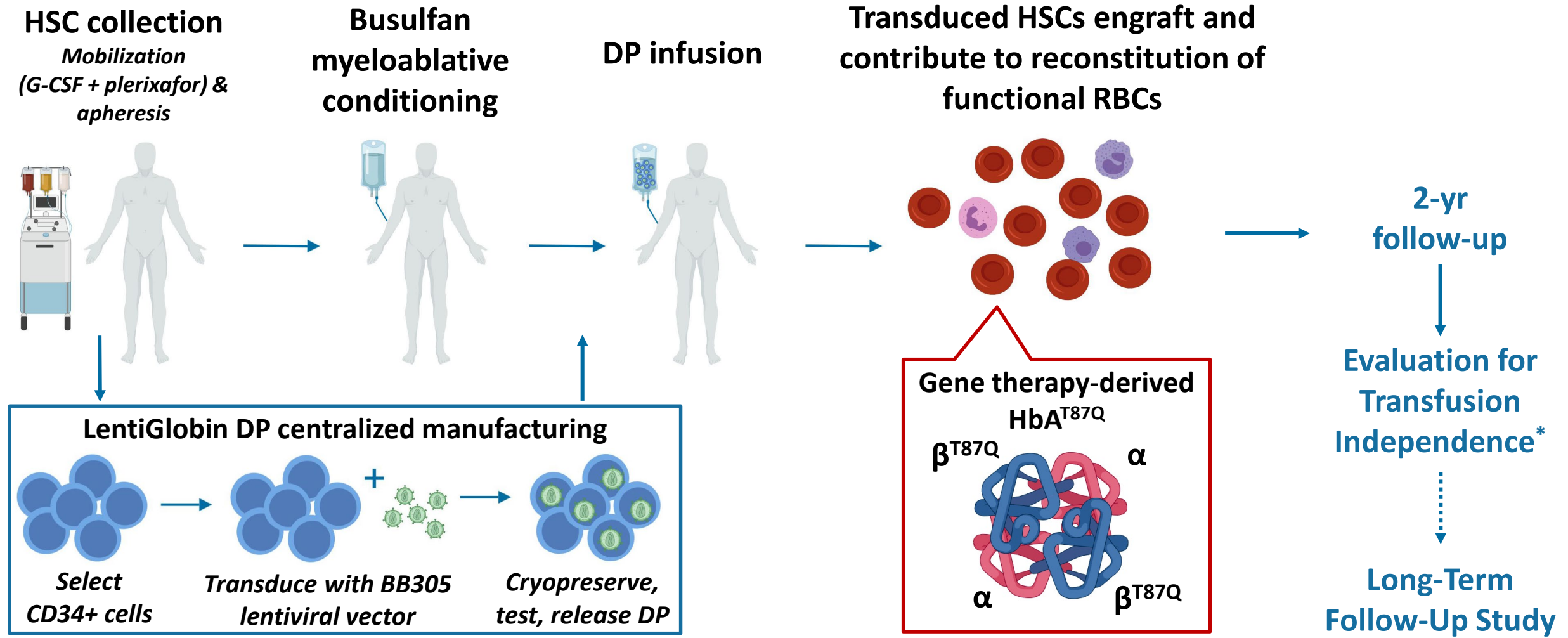


*Reason for ineligibility: 3 withdrew consent, 4 screen failures due to advanced liver disease, 1 due to ineligible genotype

[†]Patient discontinued due to positive pregnancy test

Hb, hemoglobin; TDT, transfusion-dependent β -thalassemia

HGB-207: Study design



*Transfusion Independence is defined as weighted average hemoglobin ≥ 9 g/dL without any transfusions for ≥ 12 months

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

HGB-207: Patient baseline characteristics

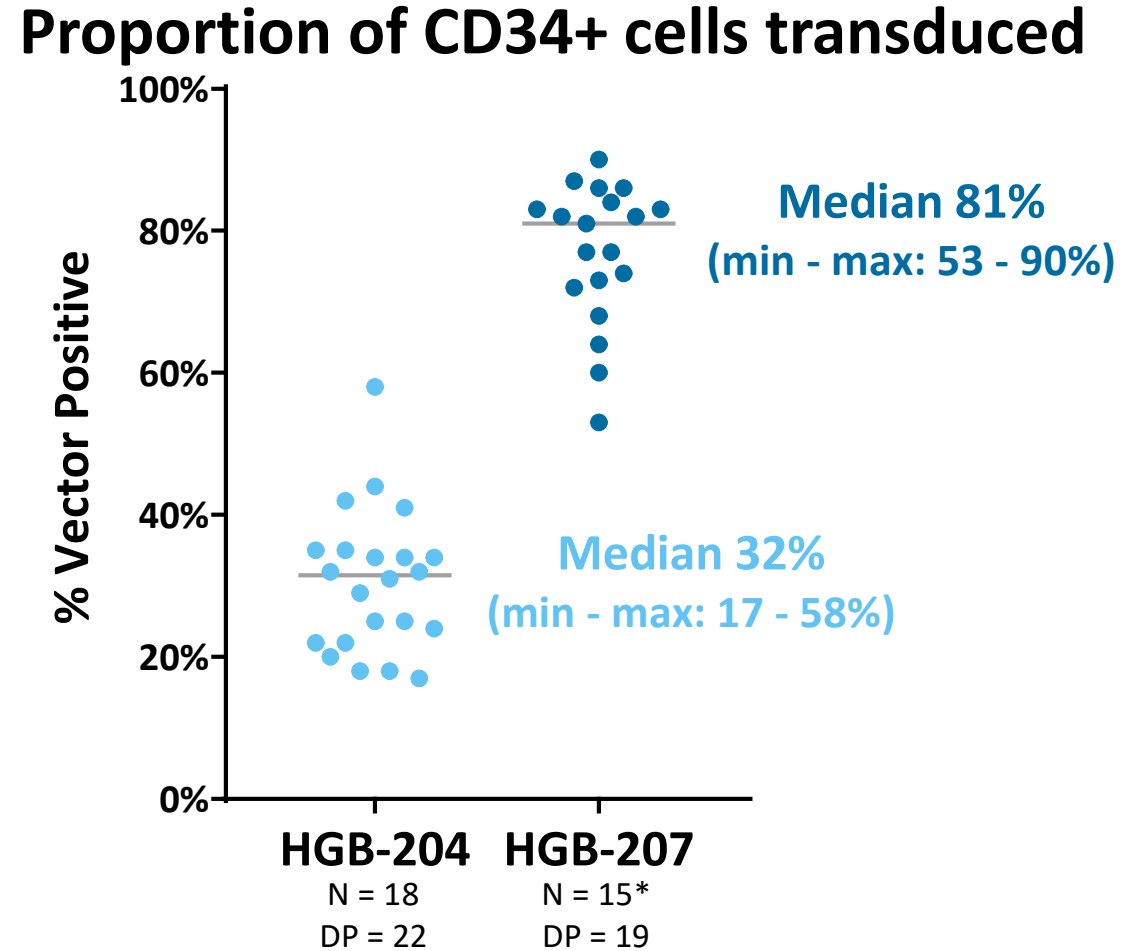
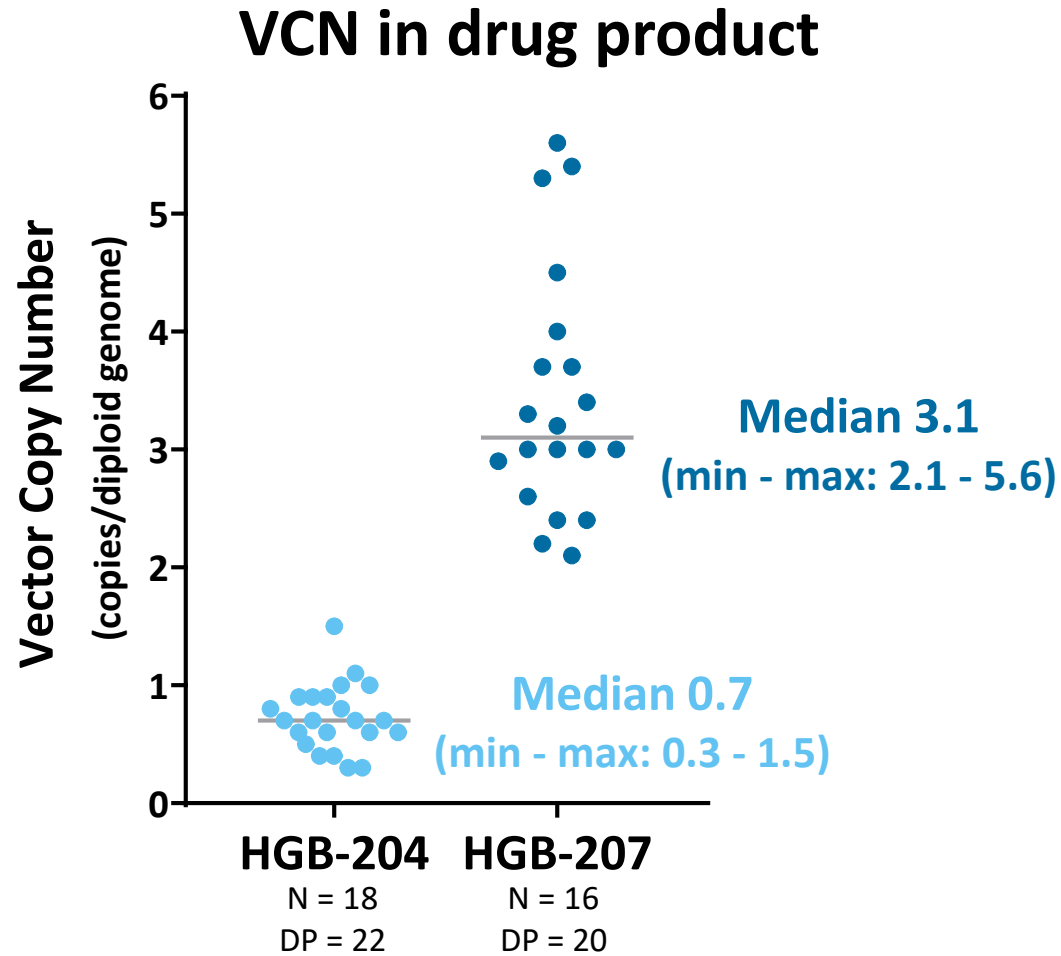
16 patients treated

Patient Characteristics		
Genotypes n, (%)	β^+/β^0	7 (43.8)
	β^E/β^0	6 (37.5)
	β^+/β^+	3 (18.8)
Gender	8 Males 8 Females	
Age at consent median (min – max), years	19 (8 – 34)	
Pre-study pRBC transfusion volume annualized median (min – max), mL/kg/yr	192.2 (152.3 – 274.4)	
Splenectomy n, %	4 (25)	

Iron Overload	
Liver iron concentration (LIC) median (min – max), mg/g	6.4 (1.0 – 41.0)
LIC < 7 mg/g n, %	8 (50)
LIC \geq 7 – < 15 mg/g n, %	4 (25)
LIC \geq 15 mg/g n, %	4 (25)
Cardiac T2* median (min – max), msec	36.5 (20.6 – 50.9)
Serum ferritin median (min – max), pmol/L	4524.5 (784 – 22517)

pRBC, packed red blood cells

HGB-207: Refined manufacturing yielded more favorable drug product characteristics



Median cell dose in HGB-207: 7.7×10^6 /kg CD34+ cells (min – max: 5.0 – 19.4)

*One %LVV+ was not available at time of datacut. Number of DP exceeds number of patients as some patients were mobilized twice. DP, drug product; VCN, vector copy number (copies/diploid genome)

HGB-207: Treatment characteristics

16 patients treated

Treatment Characteristics	
	median (min – max)
Avg daily busulfan AUC[†] μM*min	4545 (3709 – 8947)
Neutrophil engraftment[#] ANC ≥ 500 cells/μL x 3 days, days	19 (13 – 32)
Platelet engraftment[#] Platelets ≥ 20k/μL, days	44.5 (20 – 84)

[†]Estimated average daily busulfan exposure over 4 days.

[#]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.
AUC, area under the curve

HGB-207: LentiGlobin safety profile remains consistent with myeloablative conditioning

Non-hematologic grade ≥ 3 AEs* <i>Post LentiGlobin infusion in ≥ 2 patients</i>	LIC < 7 mg/g n = 8 n (%)	LIC ≥ 7 mg/g n = 8 n (%)	All patients N = 16 n (%)
Stomatitis	6 (75)	3 (38)	9 (56)
Febrile neutropenia	4 (50)	0 (0)	4 (25)
Epistaxis	1 (13)	2 (25)	3 (19)
Pyrexia	2 (25)	1 (13)	3 (19)
Veno-occlusive liver disease	2 (25)	1 (13)	3 (19)
ALT increased	2 (25)	0 (0)	2 (13)
Bilirubin increased	2 (25)	0 (0)	2 (13)
Hypoxia	2 (25)	0 (0)	2 (13)
Pharyngeal inflammation	2 (25)	0 (0)	2 (13)
Serious AEs <i>Post LentiGlobin infusion in ≥ 1 patient</i>			
Veno-occlusive liver disease	2 (25)	1 (13)	3 (19)
Hypotension	0 (0)	1 (13)	1 (6)
Hypoxia	1 (13)	0 (0)	1 (6)
Lower respiratory tract infection	0 (0)	1 (13)	1 (6)
Pyrexia	1 (13)	0 (0)	1 (6)
Sepsis	0 (0)	1 (13)	1 (6)
Thrombocytopenia	0 (0)	1 (13)	1 (6)
Transfusion reaction	1 (13)	0 (0)	1 (6)

- Due to the small population size, no clear effect of baseline LIC on the occurrence of AEs can be determined
- No graft failure or deaths
- No vector-mediated replication competent lentivirus detected to date
- No evidence of clonal dominance
- One grade 3 SAE of thrombocytopenia was considered possibly related to LentiGlobin
 - Patient had platelet counts of < 35 x10⁹/L between platelet engraftment (Day +53) and last follow-up (Month 4)

*Hematologic AEs commonly observed post-transplant have been excluded.

HGB-207: Liver veno-occlusive disease

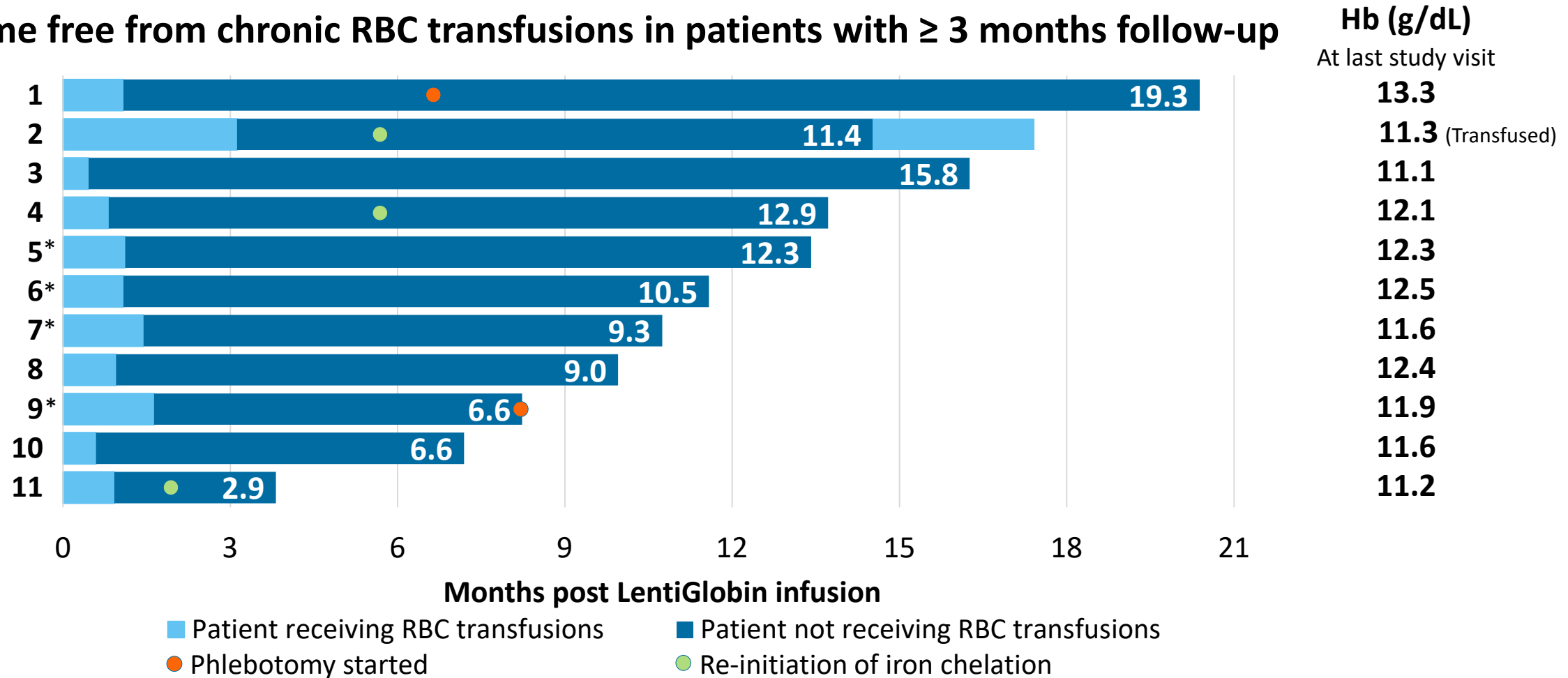
- Three grade 4, serious events of VOD were reported; all resolved after defibrotide treatment

	Patient 9	Patient 10	Patient 12	No VOD (N = 13) median (min – max)	
Age (yrs) and Gender	12 M	12 F	34 M	20 (10 – 24); 54% female (7/13)	
VOD prophylaxis	None	None	Ursodeoxycholic acid Day -8 to +38	62% (8/13)	
Screening	Imaging LIC, mg Fe/g dw	1.0	5.6	8.5	7.2 (1.4 – 41.0)
	AST, U/L	23	14	40	21 (17 – 67)
	ALT, U/L	32	7	43	24 (9 – 164)
	Total bilirubin, μmol/L	20.9	22.9	25.3	36.8 (13.9 – 96.8)
Average busulfan AUC,[†] μM*min	4595	4471	4545	4428 (3709 – 8947)[‡]	
Busulfan dosing schedule	Q 24 hrs	Q 24 hrs	Q 24 hrs	58% Q 24 hrs (7/12)[‡] 42% Q 6 hrs (5/12)[‡]	
Busulfan dose adjustment	One increase and one decrease in dose	One increase in dose	One decrease in dose	42% 1 increase and 1 decrease (5/12)[‡] 25% ≥ 1 increase (3/12)[‡] 25% ≥ 1 decrease (3/12)[‡] 8% no dose change (1/12)[‡]	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; VOD, liver veno-occlusive disease. [†]Estimated average daily busulfan exposure over 4 days. Target busulfan AUC of 1100 (min - max 1000 - 1250) μM*min for every 6 hours dosing, or 4500 (min - max 4000 – 5000) μM*min for once daily dosing. After protocol amendment, target busulfan AUC was reduced to 1050 (min - max 950 - 1125) μM*min for every 6 hours dosing, or 4200 (min - max 3800 – 4500) μM*min for once daily dosing. [‡]N=12, Busulfan conditioning regimen was not available for one patient at time of data snapshot.

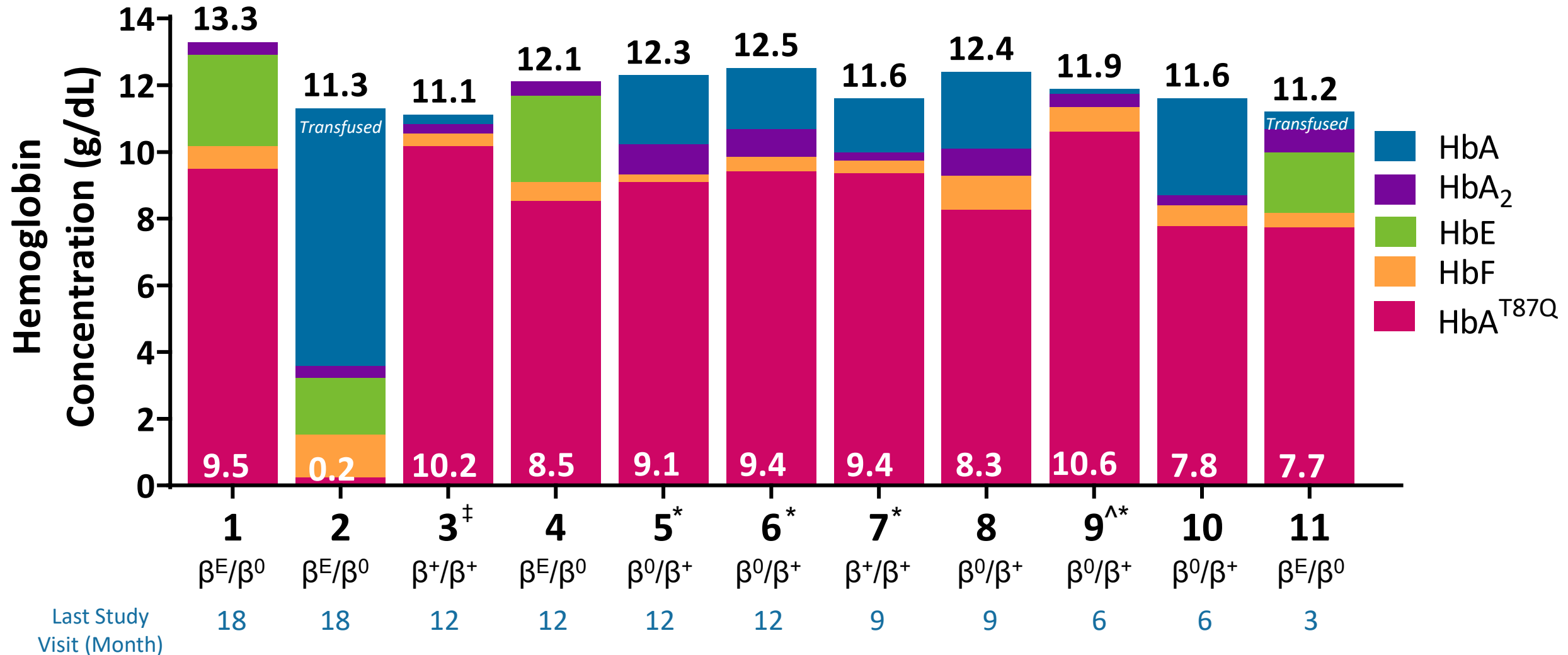
HGB-207: 10/11 patients are transfusion free with Hb > 11 g/dL

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



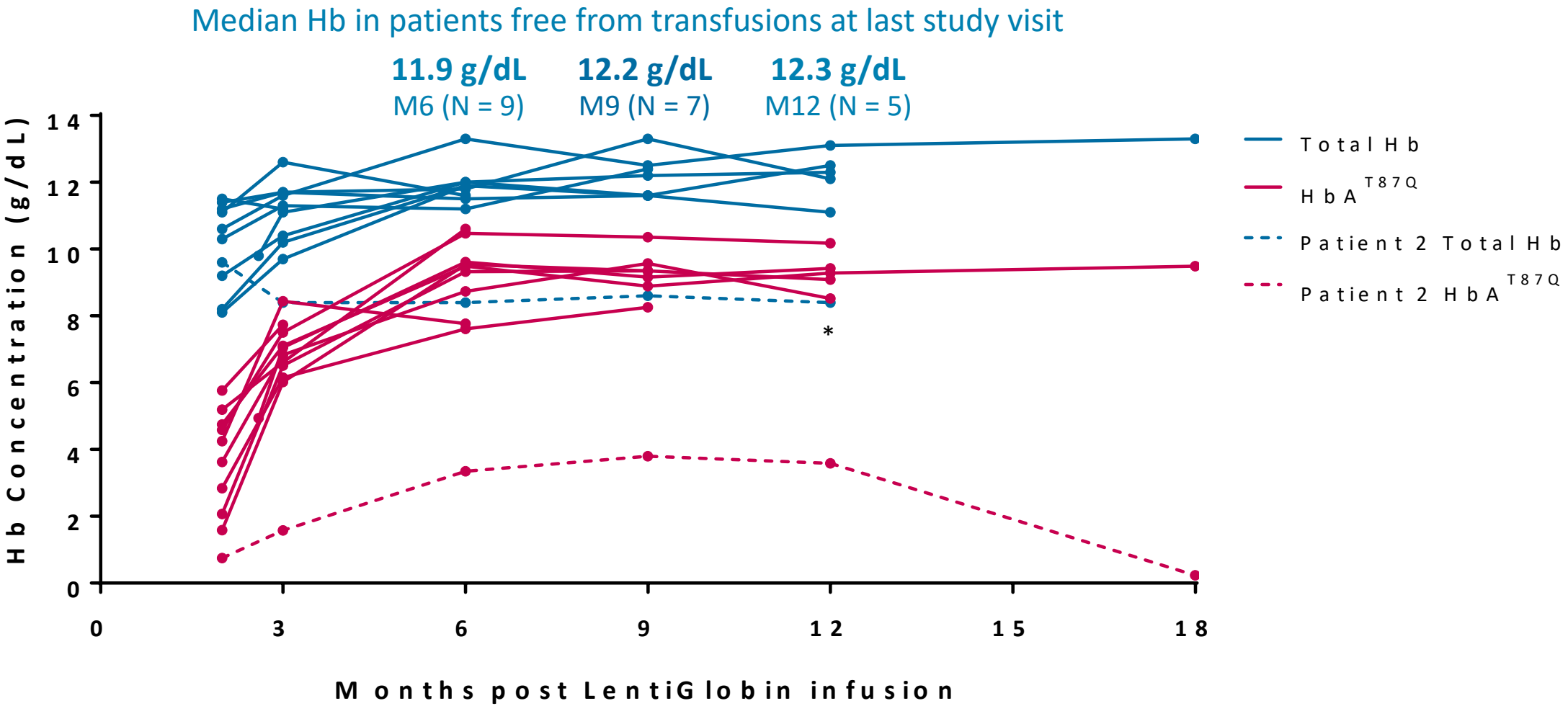
Patients 1 and 3 have achieved the protocol definition of transfusion independence
 (Weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months)

HGB-207: Gene therapy-derived HbA^{T87Q} significantly contributes to total Hb in 10/11 patients



*Male patients; [‡]Patient is homozygous for IVS-I-5 β -globin mutation; [^]Patient is heterozygous for IVS-I-5 β -globin mutation. Hb, hemoglobin

HGB-207: Total Hb and gene therapy-derived HbA^{T87Q} remain stable in patients free from transfusions

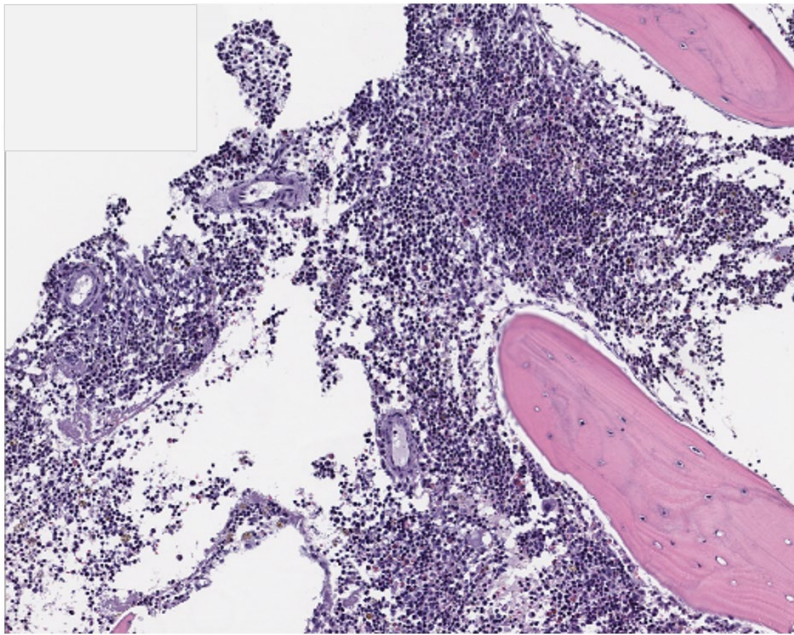


*Last Hb before patient restarted red blood cell transfusions; Hb, hemoglobin

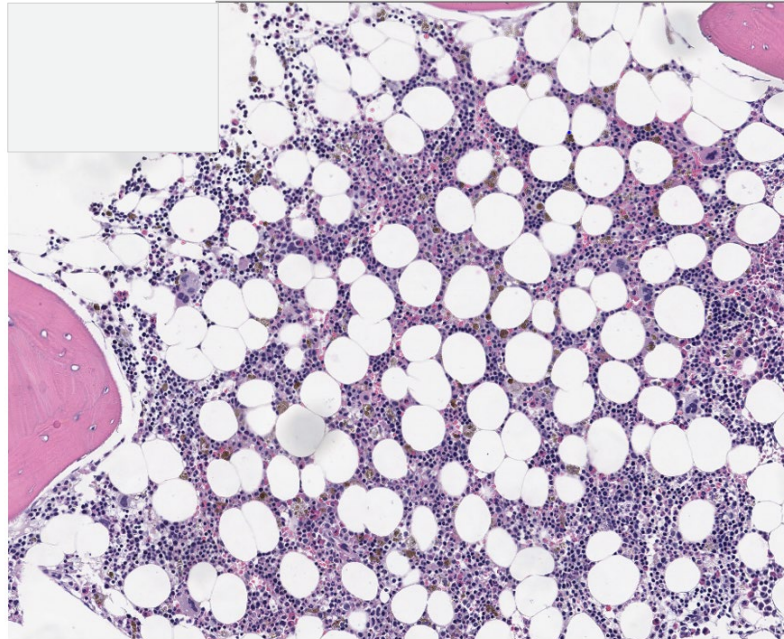
HGB-207: Improvement in erythropoiesis following LentiGlobin gene therapy

Patient 1 (20 yrs old) bone marrow analysis

Screening

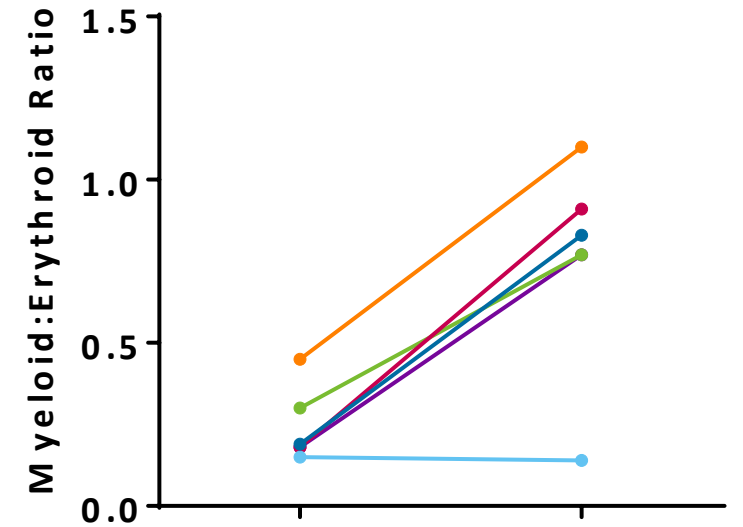


Month 12 post-LentiGlobin



Hb at Month 12: 13.1 g/dL

Myeloid:Erythroid ratio following LentiGlobin gene therapy



Screening Month 12

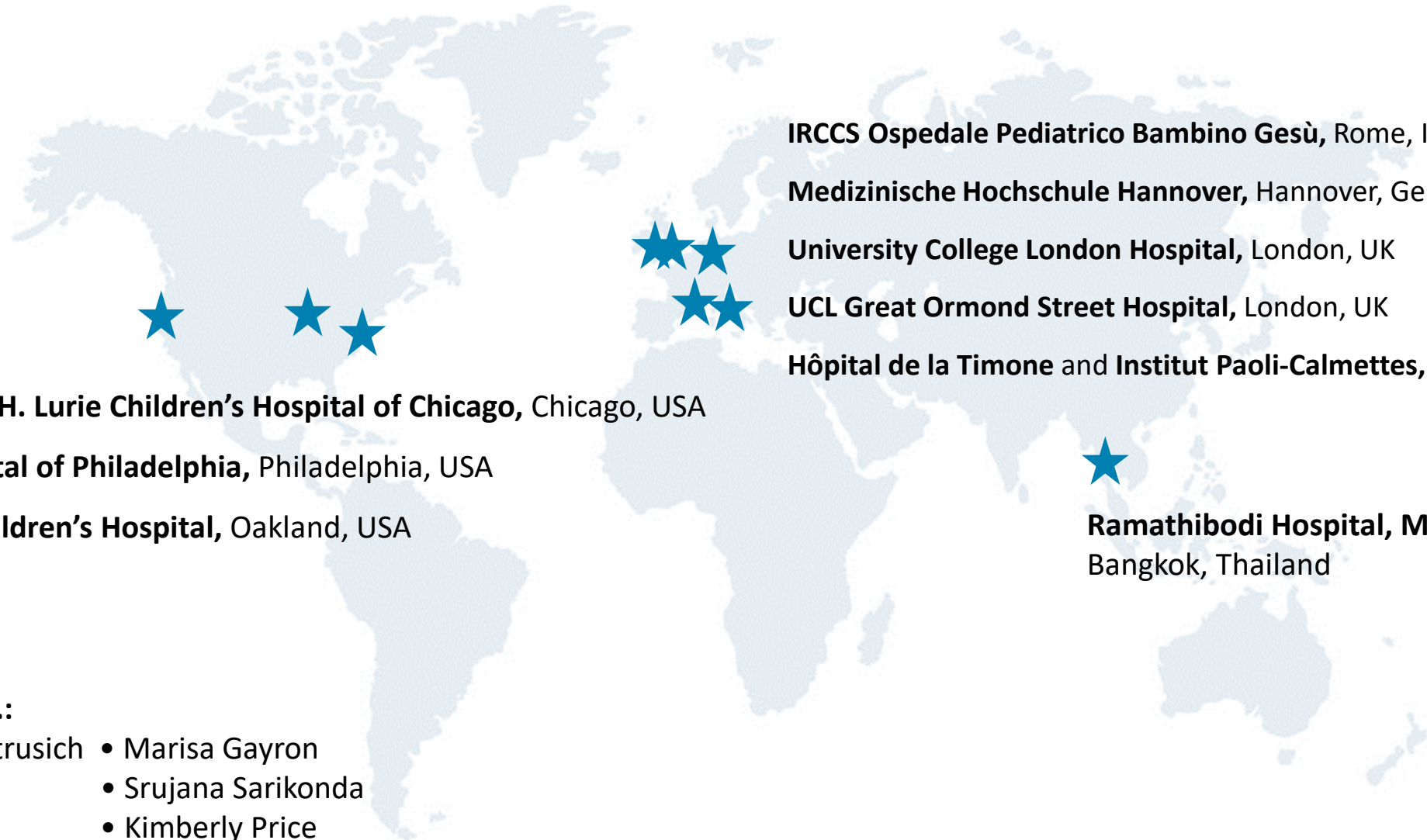
- 1 2
- 3 4
- 5 6

Normal M:E Ratio¹: 3-4:1

HGB-207: Summary

- LentiGlobin gene therapy enabled most patients with TDT and non- β^0/β^0 genotypes to stop blood transfusions with results maintained through up to 20 months of follow-up
 - 2/3 patients with sufficient follow-up have achieved the primary endpoint of transfusion independence
 - 10/11 patients with ≥ 3 months follow-up have stopped chronic blood transfusions
 - Total Hb of 11.1 – 13.3 g/dL consisting of 7.7 – 10.6 g/dL gene therapy-derived Hb, HbA^{T87Q}, at last visit
- Bone marrow morphology indicates improvements in erythropoiesis
- The safety profile remains generally consistent with myeloablative busulfan conditioning, including SAEs of liver veno-occlusive disease
 - Some patients experienced delayed platelet engraftment
 - One SAE of grade 3 thrombocytopenia was considered possibly related to LentiGlobin
- MAA under review by EMA for the treatment of adults and adolescents with TDT and non- β^0/β^0 genotypes

Thank you to the study participants and their families



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