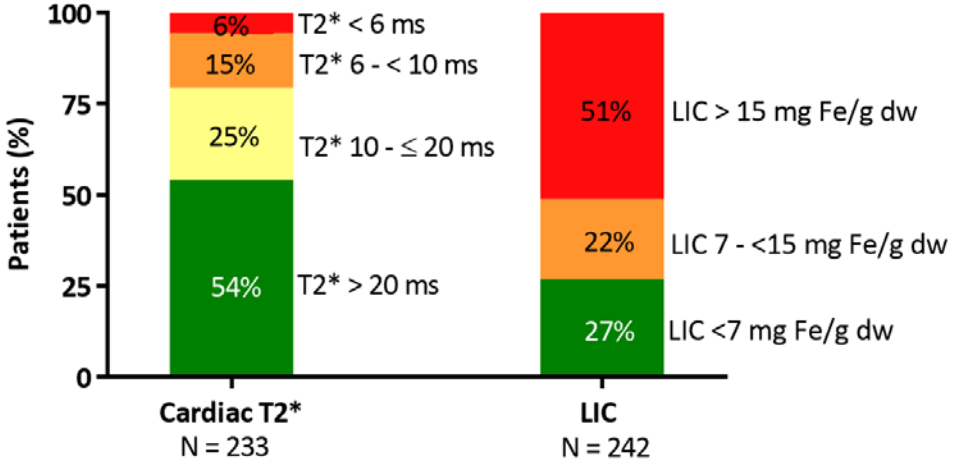
EHA 2018 Abstract 1510

LentiGlobin gene therapy for transfusion-dependent β-thalassemia (TDT) in patients with non-β^0/β^0 genotypes: Updated results from Northstar-2

Franco Locatelli, Mark C. Walters, Janet L. Kwiatkowski, John E. J. Rasko, Suradej Hongeng, Gary J. Schiller, John Porter, Martin Sauer, Adrian J. Thrasher, Isabelle Thuret, Heidi Elliot, Briana Deary, Marisa Gayron, Mohammed Asmal, Alexis A. Thompson

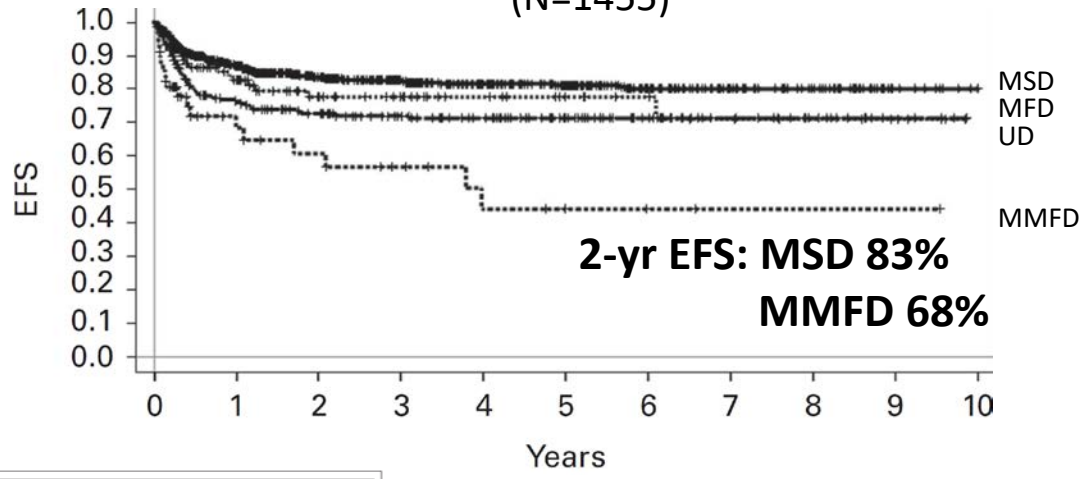
Gene therapy for transfusion-dependent β-thalassemia (TDT)

Iron overload in transfusion-dependent anemias[1]



Event free survival in thalassemia patients following HSCT[2]

(N=1455)



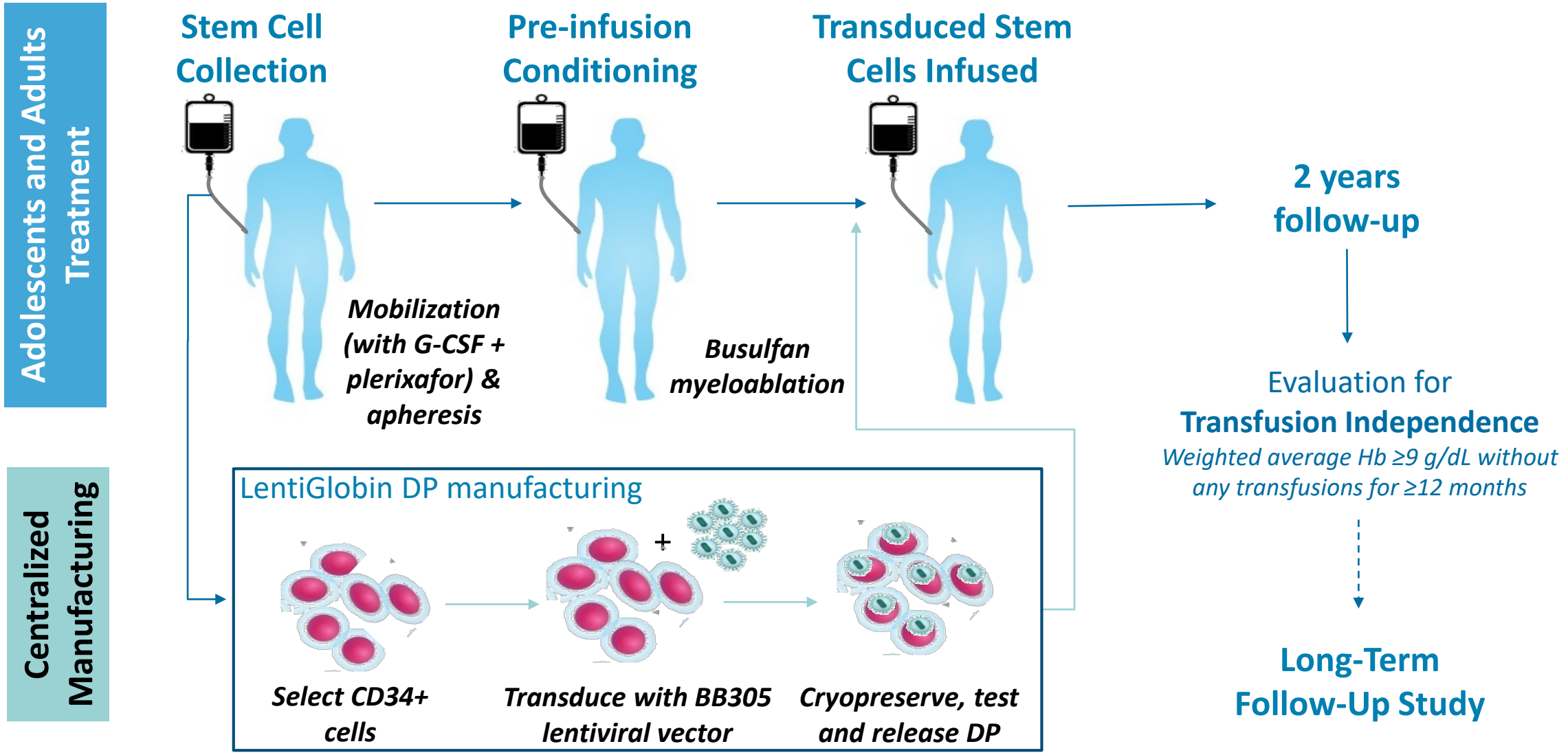
2-yr EFS: MSD 83%
MMFD 68%

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

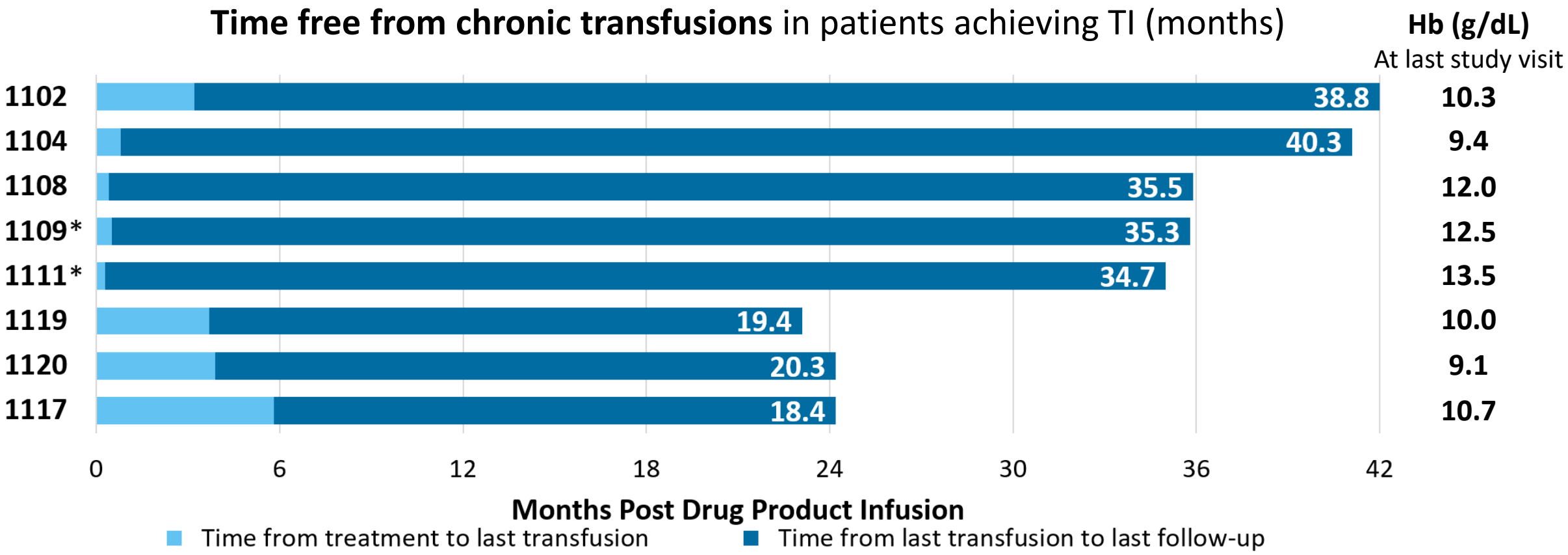
A.A. Thompson, M.C. Walters, J. Kwiatkowski, J.E.J. Rasko, J.-A. Ribeil, S. Hongeng, E. Magrin, G.J. Schiller, E. Payen, M. Semeraro, D. Moshous, F. Lefrere, H. Puy, P. Bourget, A. Magnani, L. Caccavelli, J.-S. Diana, F. Suarez, F. Monpoux, V. Brousse, C. Poirot, C. Brouzes, J.-F. Meritet, C. Pondarré, Y. Beuzard, S. Chrétien, T. Lefebvre, D.T. Teachey, U. Anurathapan, P.J. Ho, C. von Kalle, M. Kletzel, E. Vichinsky, S. Soni, G. Veres, O. Negre, R.W. Ross, D. Davidson, A. Petrusich, L. Sandler, M. Asmal, O. Hermine, M. De Montalembert, S. Hacein-Bey-Abina, S. Blanche, P. Leboulch, and M. Cavazzana

1. Aydinok et al. *Eur J Haematol*. 2015;95(3):244-53. 2. Baronciani et al. *Bone Marrow Transplant*. 2016;51(4):536-41. 3. Thompson et al. *N Engl J Med*. 2018 Apr 19;378(16):1479-1493.

Phase 1/2 HGB-204 (Northstar) and Phase 3 HGB-207 (Northstar-2) study designs



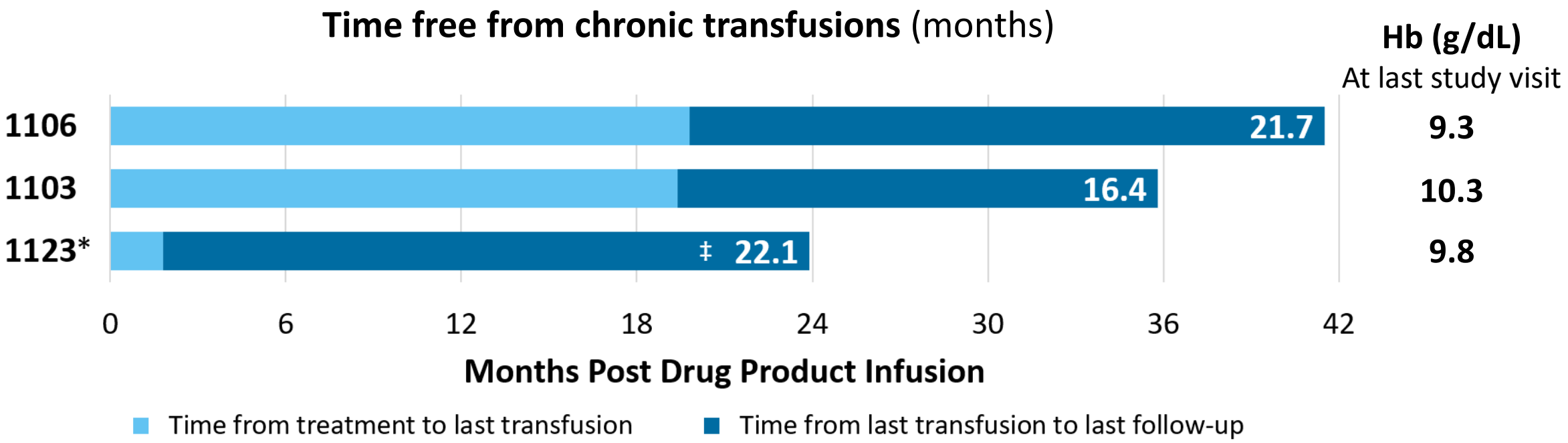
HGB-204: 8/10 patients with non-β^0/β^0 genotypes achieved and maintain transfusion independence (TI)



- **Median duration of transfusion independence** to date of **33 months** (min – max: 16 – 38)
- **Reduction in annualized transfusion volume** in 2/10 patients not achieving TI: **27%, 82%**

*Indicates male patients. Transfusion independence (TI) is defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months. Hb, hemoglobin

HGB-204: Transfusion status of patients with β^0/β^0 genotypes



- **3/8 patients are free from chronic transfusions**
- 2/8 patients achieved **transfusion independence** with a **median duration** to date of **15 months** (min – max: 14 – 16)
- Median **reduction in annualized transfusion volume** in patients receiving transfusions (5/8): **53%** (min – max: 8% – 74%)

*Indicates male patients. ‡Patient had a single transfusion for an acute event of cat scratch disease.
Transfusion independence is defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months. Hb, hemoglobin

HGB-204: Safety of LentiGlobin treatment in adults and adolescents with TDT remains consistent with myeloablative conditioning

Non-hematologic* grade ≥ 3† AEs reported in ≥2 patients *DP infusion to 2 years follow-up*	**n (%)** **N=18**
Stomatitis	12 (67)
Febrile neutropenia	10 (56)
Pharyngeal inflammation	5 (28)
Menstruation irregular	3 (17)
Epistaxis	2 (11)
Veno-occlusive liver disease‡	2 (11)
Serious AEs* reported in ≥2 patients *DP infusion to last follow-up*	
Thrombosis§	2 (11)
Veno-occlusive liver disease‡	2 (11)

*Hematologic AEs commonly observed post-transplant have been excluded; †No grade 4 or 5 non-hematologic events were reported; ‡ Both VODs were grade 3 and serious events §Included 1 vena cava thrombosis and 1 intracardiac thrombus

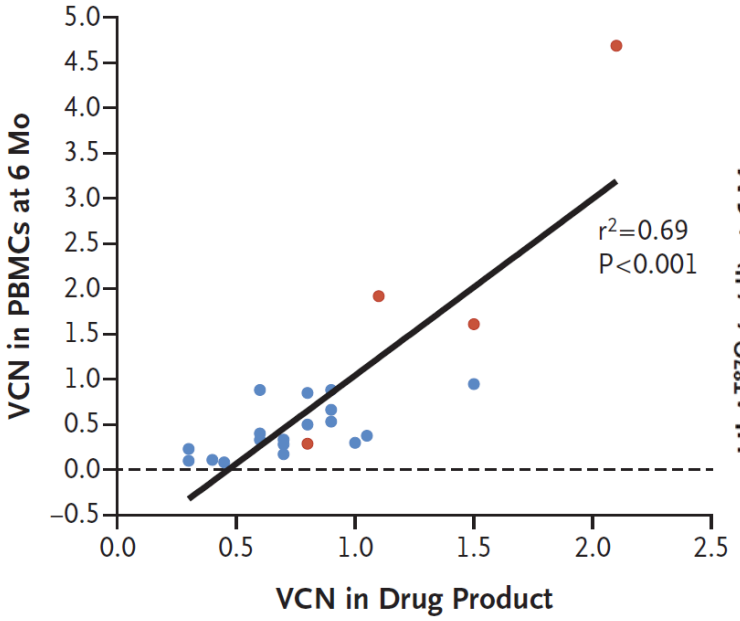
- One SAE of wild-type HIV infection was reported 23 months after DP infusion and was considered not related to LentiGlobin

- No grade ≥ 3 DP-related AEs
- No graft failure
- No vector-mediated replication competent lentivirus detected to date
- No evidence of clonal dominance

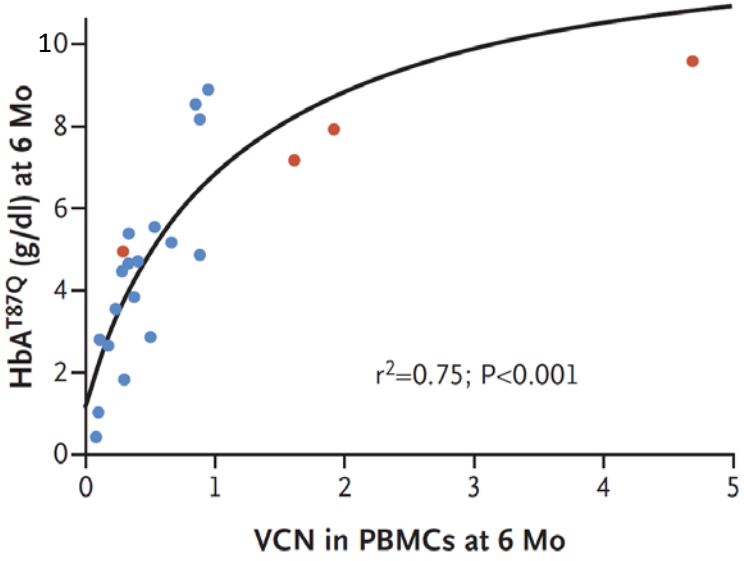
AE, adverse event; DP, drug product; HIV, human immunodeficiency virus; SAE, serious adverse event, VOD, veno-occlusive liver disease

HGB-207 Phase 3 study initiated to evaluate effect of higher VCNs in patients with non-β^0/β^0 genotypes

Drug product VCN correlated with peripheral VCN[1]



Peripheral VCN correlated with HbA^{T87Q} levels[1]



HGB-207 Study Status

Consented
N=26
- Ineligible N=6*

Stem Cell Mobilization
N=17
- Discontinued N=1†

Drug Product Release
N=12
- Transplant Pending N=1

LentiGlobin Infused
N=11
Adults & adolescents

Blue: HGB-204; Red: HGB-205 (NCT02151526)
*Reason for ineligibility: 2 withdrew consent, 4 screen failures due to advanced liver disease
†Patient discontinued due to positive pregnancy test
HbA^{T87Q}, vector derived hemoglobin; PBMC, peripheral blood mononuclear cells; VCN, vector copy number (copies per diploid genome)

1. Thompson et al. *N Engl J Med*. 2018 Apr 19;378(16):1479-1493.

HGB-207: Patient and treatment characteristics

in 11 patients treated

Patient Characteristics

Genotypes n, (%)	β^+/β^0 β^E/β^0 β^+/β^+	**5** (45) **4** (36) **2** (18)
Gender		**7 Females**
Age at consent median (min–max), years		**20** (12 – 24)
Pre-study pRBC transfusion volume annualized median (min–max), mL/kg/yr		**192.9** (158.7 – 251.3)
Liver iron concentration median (min–max), mg/g		**5.6** (1.0 – 41.0)
Cardiac T2* median (min–max), msec		**36.7** (20.6 – 50.9)
Splenectomy n, %		**3** (27)

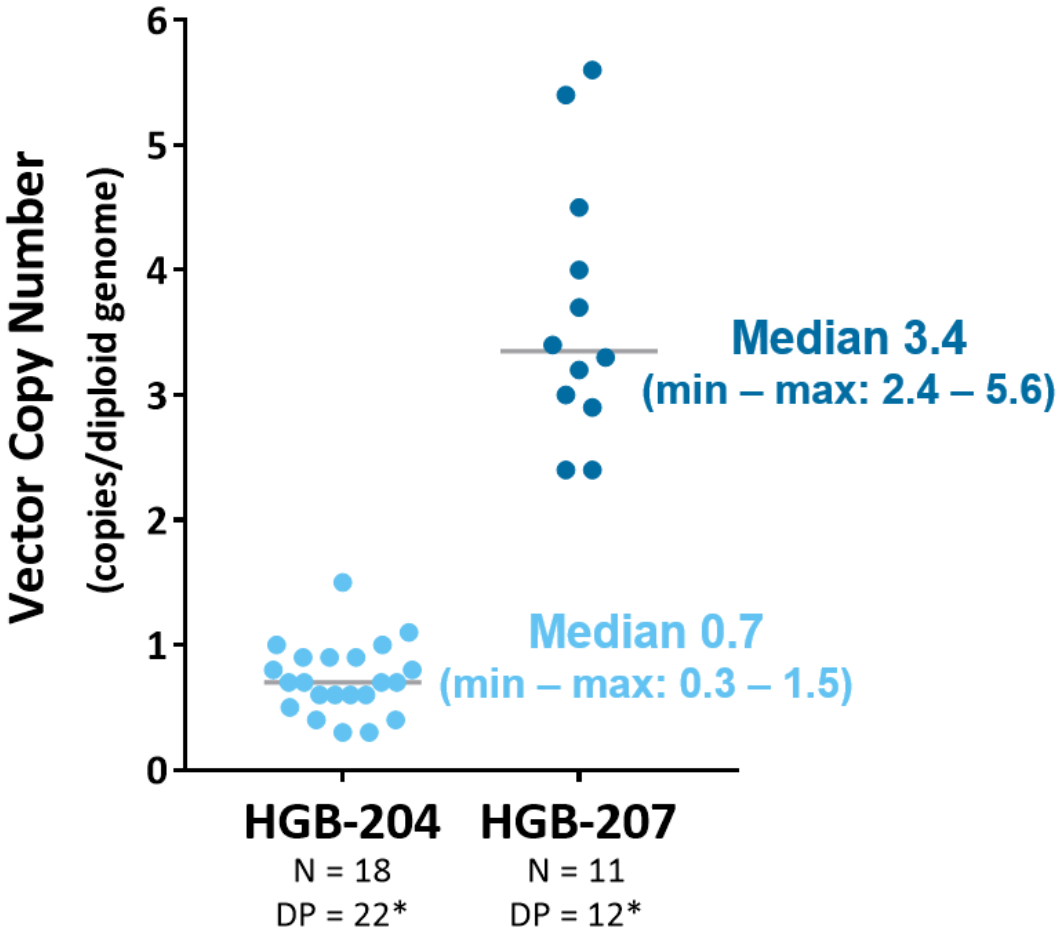
Treatment Characteristics

	median (min – max)
Busulfan AUC[†] µM*min	**4471** (3709 – 5789)
Drug product cell dose CD34+ cells x 10^6/kg	**7.4** (5.0 – 19.4)
Neutrophil engraftment[‡^] study day	**21.5** (16 – 28)
Platelet engraftment[#^] study day	**44.5** (34 – 84)
Duration of hospitalization[§^] days	**44.5** (32 – 92)
Follow-up month	**8.5** (0.3 – 16.2)

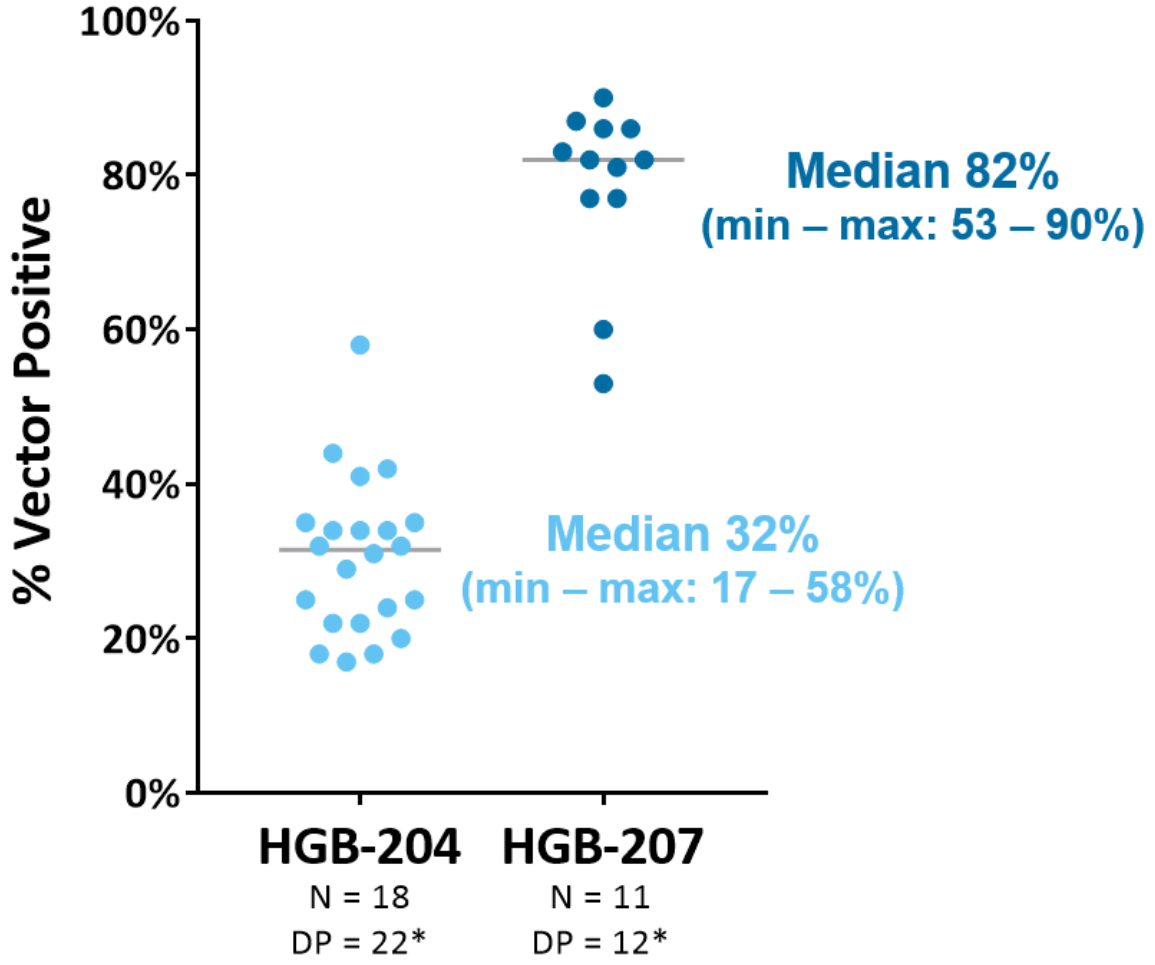
[†]Estimated average daily busulfan exposure over 4 days; [‡]ANC ≥500 cells/µL for 3 consecutive days; [#]Unsupported platelet count ≥ 20,000/µL; [§]Initiation of hospitalization from conditioning to post drug product infusion discharge; [^]N=10, 1 patient with 0.3 months follow-up had not engrafted and remains hospitalized as of data-cut off date.
ANC, absolute neutrophil count; AUC, area under the curve; DP, drug product; pRBC, packed red blood cells; TDT, transfusion-dependent β-thalassemia.

Refined manufacturing consistently yielded more favorable drug product characteristics

VCN in drug product



Proportion of CD34+ cells transduced



*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: Safety profile post DP infusion remains consistent with myeloablative conditioning

Non-hematologic* grade ≥3 AEs Post DP infusion in ≥2 patients	**n (%)** N = 11
Stomatitis	6 (55)
Febrile neutropenia	3 (27)
Pyrexia	3 (27)
ALT increased	2 (18)
Bilirubin increased	2 (18)
Epistaxis	2 (18)
Hypoxia	2 (18)
Veno-occlusive liver disease	2 (18)
Serious AEs* Post DP infusion in ≥1 patient	
Veno-occlusive liver disease	2 (18)
Hypotension	1 (9)
Hypoxia	1 (9)
Sepsis	1 (9)
Transfusion reaction	1 (9)

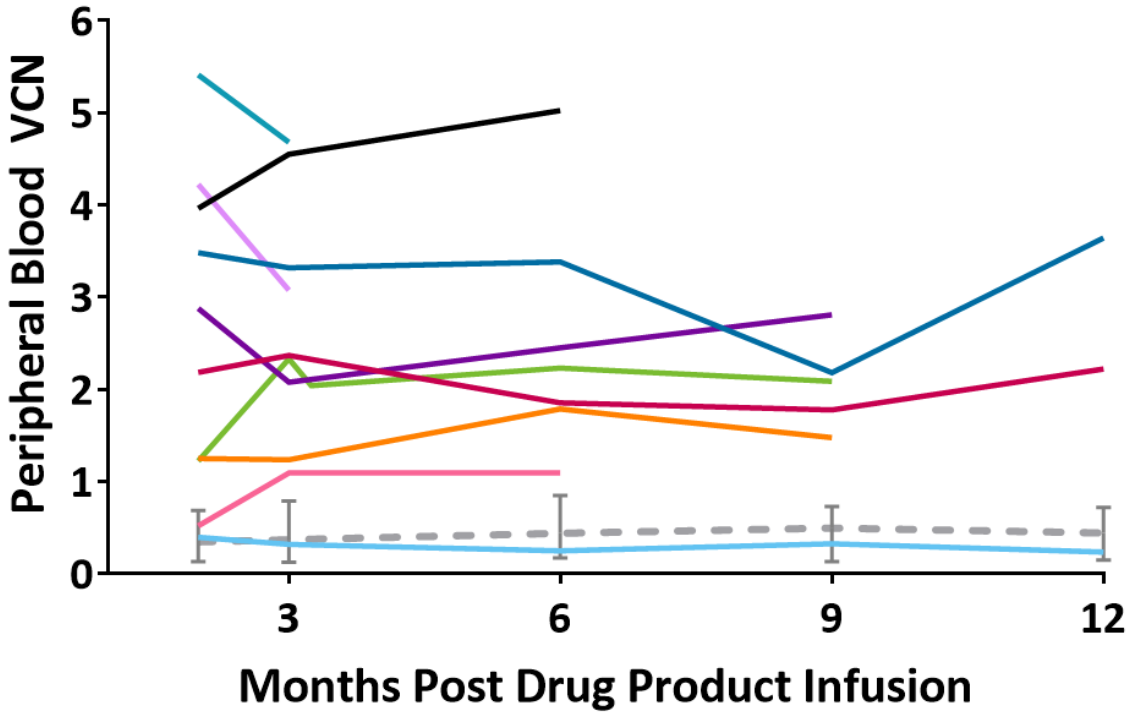
- One grade 1 AE of abdominal pain was considered related to LentiGlobin
- Two SAEs of grade 4 VOD extended hospitalization following DP infusion
  - Events occurred on Day +23 and Day +34
  - Both patients were treated with defibrotide
  - Both events have resolved

- No graft failure
- No deaths
- No vector-mediated replication competent lentivirus detected to date
- No early evidence of clonal dominance

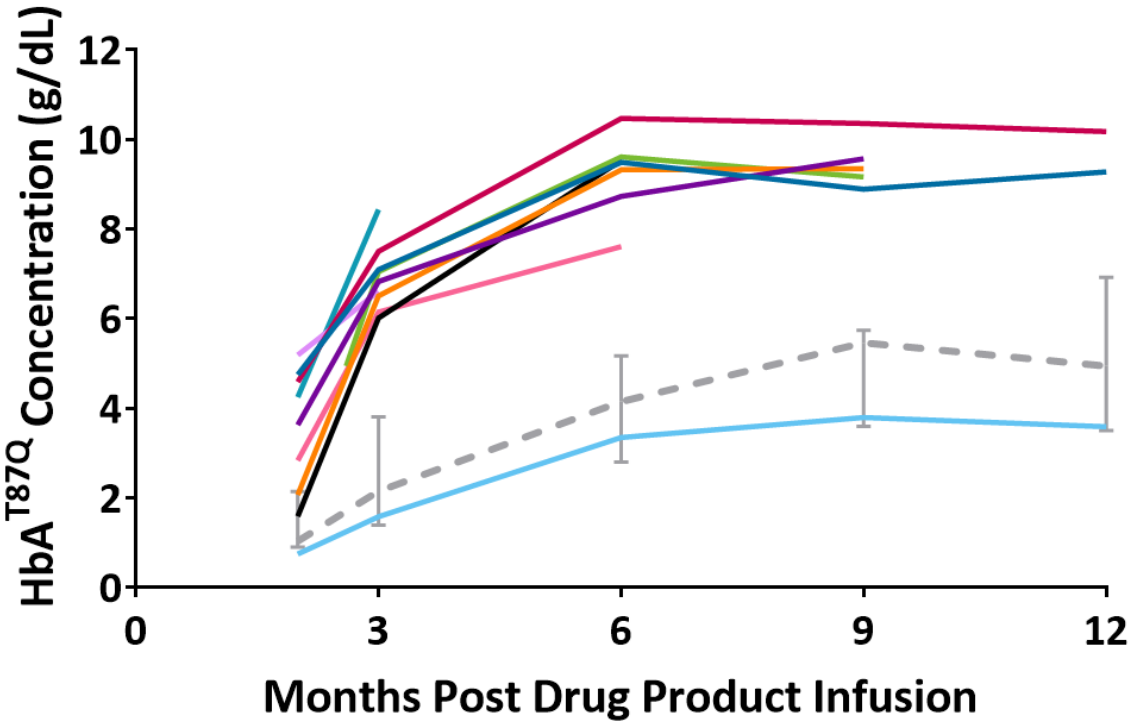
*Hematologic AEs commonly observed post-transplant have been excluded; AEs, adverse events; ALT, alanine aminotransferase; DP, drug product; SAE, serious AE; VOD, veno-occlusive liver disease

HGB-207: Peripheral blood VCN and HbA^{T87Q} production over time

Peripheral blood VCN over time



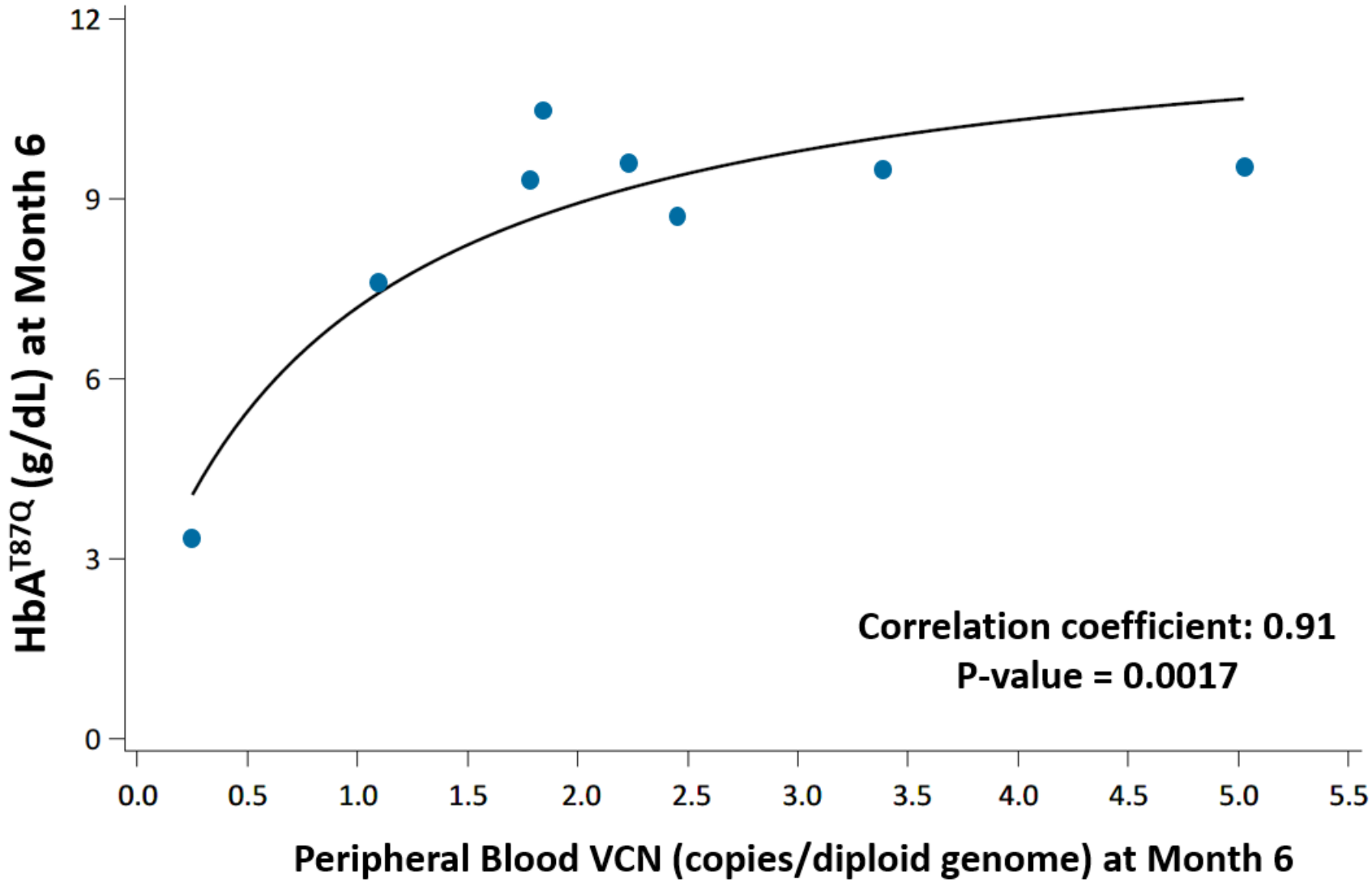
HbA^{T87Q} production over time



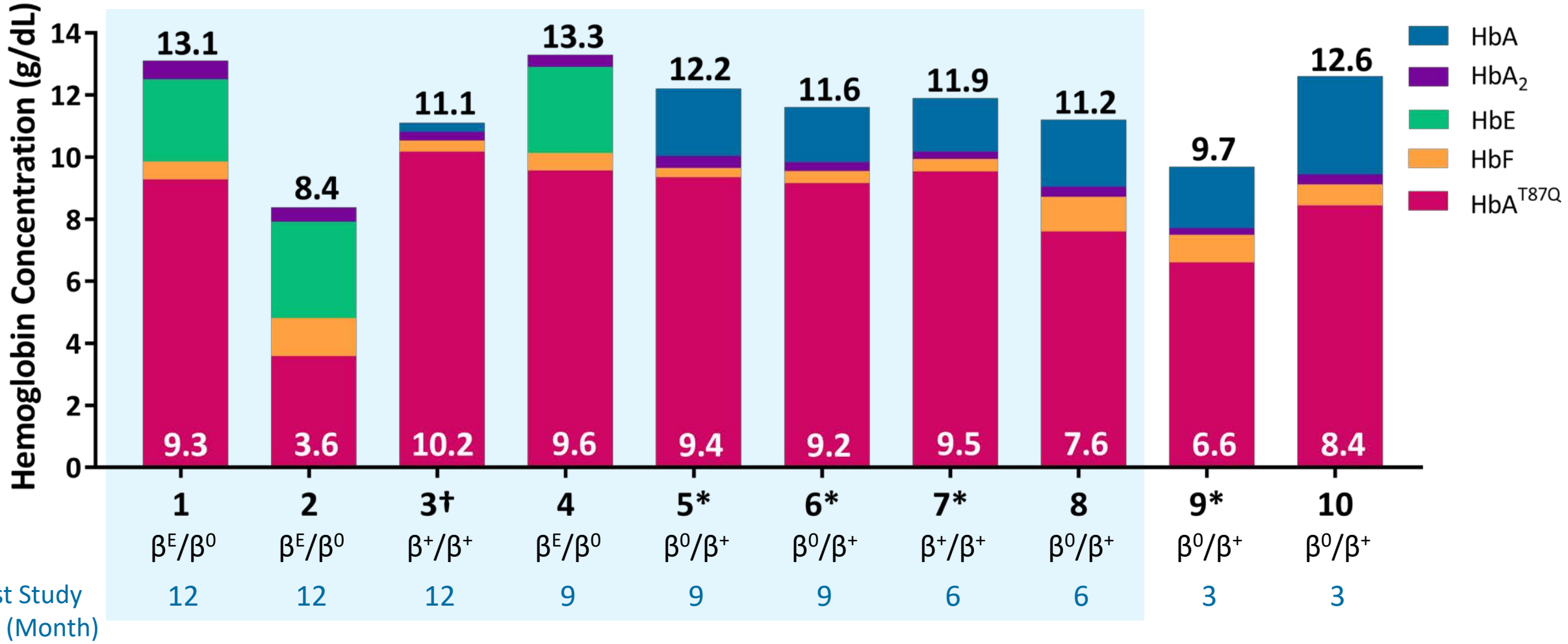
HGB-204 non-β^0/β^0 HGB-207: 1 3 5 7 9 2 4 6 8 10

For 204 non-β^0/β^0 patients, medians (Q1, Q3) depicted. HbA^{T87Q}, vector derived hemoglobin VCN, vector copy number (copies/diploid genome)

HGB-207: Stronger correlation between peripheral blood VCN and HbA^{T87Q} observed with higher DP VCNs

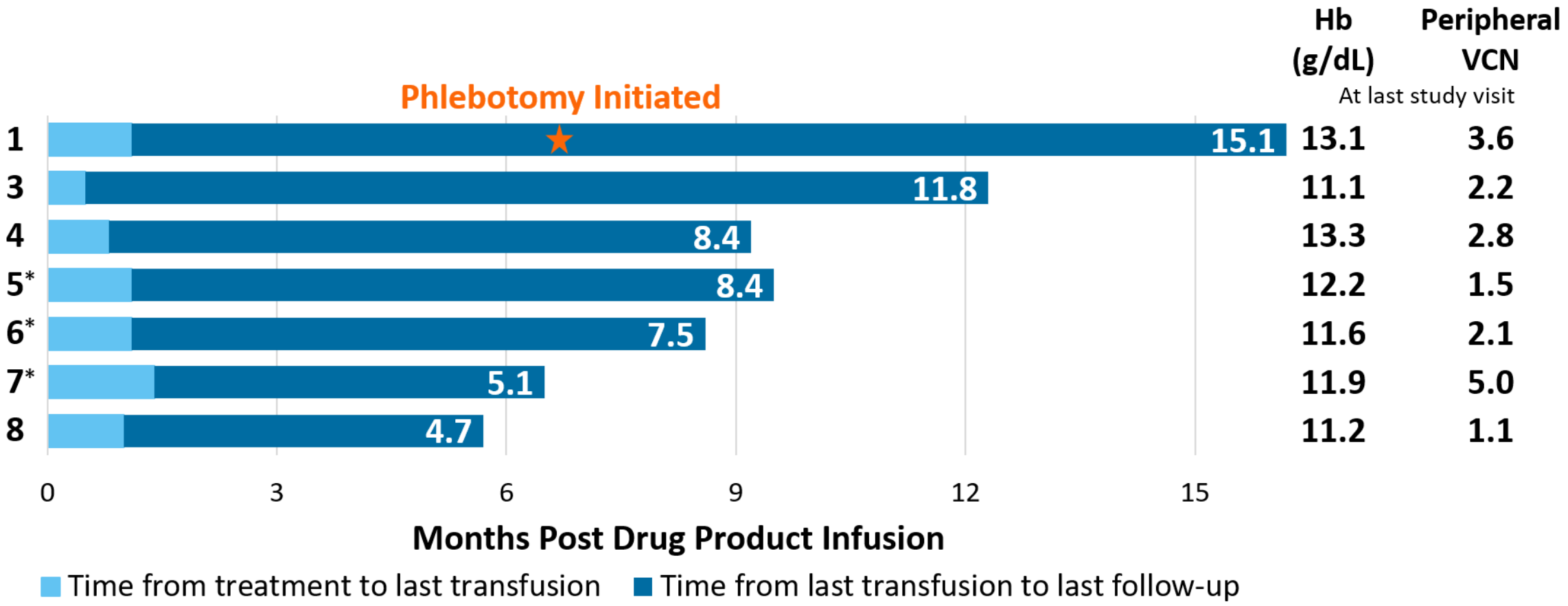


HGB-207: 7/8 patients are producing ≥ 7.6 g/dL of HbA^{T87Q} by 6 months



* Indicates male patients; †Patient is homozygous for severe IVS-1-5 β-globin mutation

HGB-207: 7/8 patients with ≥ 6 months follow-up are transfusion free with unsupported Hb 11.1 – 13.3 g/dL



- **First treated patient achieved transfusion independence and has begun phlebotomy**
- Patient 2: no transfusions for 11 months, then transfused due to low Hb with peripheral VCN 0.2

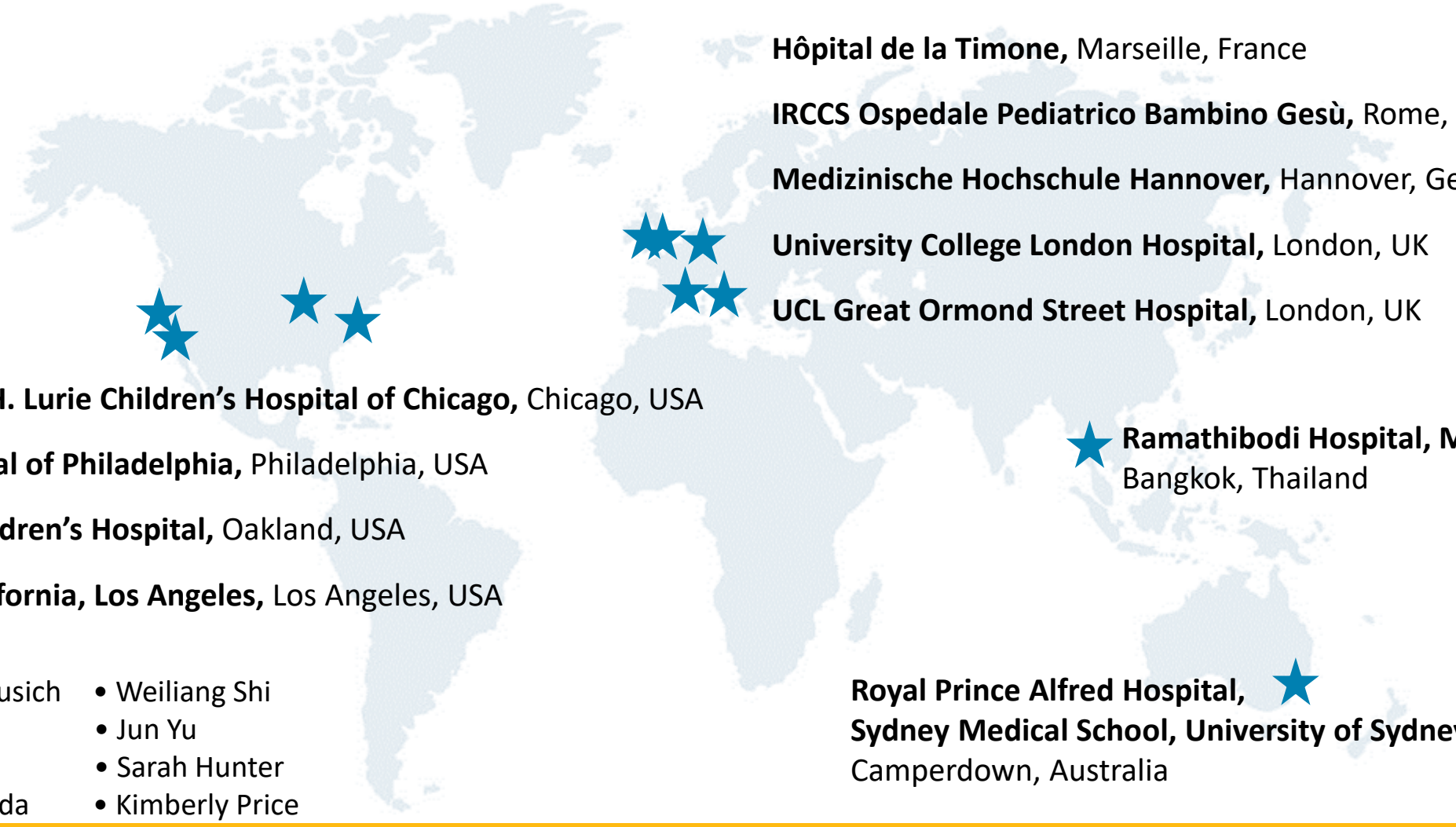
*Indicates male patients; Transfusion independence is defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months; Hb, hemoglobin; VCN, vector copy number

Summary

- 2-year Phase 1/2 Northstar (HGB-204) study of LentiGlobin gene therapy for TDT is complete
  - 8/10 patients with non-β^0/β^0 genotypes and 2/8 patients with β^0/β^0 genotypes have achieved transfusion independence
- LentiGlobin manufacturing refinements consistently yield more favorable drug product characteristics
  - Higher median DP VCN (3.4 vs 0.7) and transduced CD34+ cells (82% vs 32%) in Northstar-2 vs Northstar
- In the Phase 3 Northstar-2 (HGB-207) study of patients with TDT and non-β^0/β^0 genotypes:
  - 7/8 patients with ≥ 6M follow-up have stopped chronic transfusions
  - These 7 patients have 7.6 – 10.2 g/dL HbA^{T87Q} and are maintaining total Hb 11.1 – 13.3 g/dL
- Safety profile in both studies is consistent with myeloablative conditioning with busulfan
  - No grade ≥ 3 AEs were considered related to LentiGlobin
- Efficacy and safety of LentiGlobin in patients with TDT and β^0/β^0 genotypes is currently being evaluated in the Phase 3 Northstar-3 (HGB-212) study

AE, adverse event; Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence; VCN, vector copy number (copies/diploid genome)

HGB-204 and HGB-207: Study sites and investigators



Hôpital de la Timone, Marseille, France

IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

Medizinische Hochschule Hannover, Hannover, Germany

University College London Hospital, London, UK

UCL Great Ormond Street Hospital, London, UK

Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, USA

Children's Hospital of Philadelphia, Philadelphia, USA

UCSF Benioff Children's Hospital, Oakland, USA

University of California, Los Angeles, Los Angeles, USA

Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

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

bluebird bio, Inc.:

- Alexandria Petrusich
- Ying Chen
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- Srujana Sarikonda
- Weiliang Shi
- Jun Yu
- Sarah Hunter
- Kimberly Price

Thank you to the study participants and their families

Back-up

One SAE of asymptomatic wild-type HIV infection was reported

- Patient was found to have an HIV-1 infection on a surveillance HIV-1 western blot assay 23 months following treatment with LentiGlobin
- An HIV-1 western blot 12 months following LentiGlobin infusion was negative
- The infection was considered not related to LentiGlobin
  - HIV-1 western blot identified the patient had antibodies to multiple components of the HIV-1 envelope which are not part of the LentiGlobin BB305 vector
  - RCL VSV-G assay was negative
    - Assay looks for evidence of the VSV-G envelope found in the LentiGlobin BB305 vector and not in wild type HIV-1

HIV, human immunodeficiency virus; RCL, replication competent lentivirus