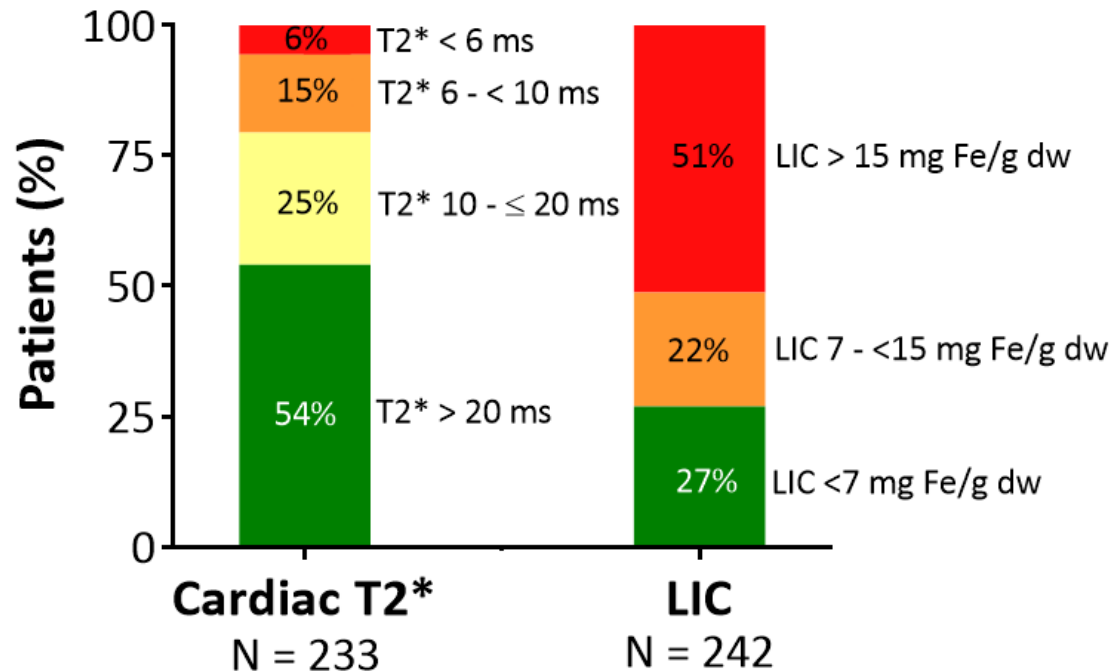


Clinical Outcomes Following LentiGlobin Gene Therapy for Transfusion-Dependent β -thalassemia in the Northstar HGB-204 Study

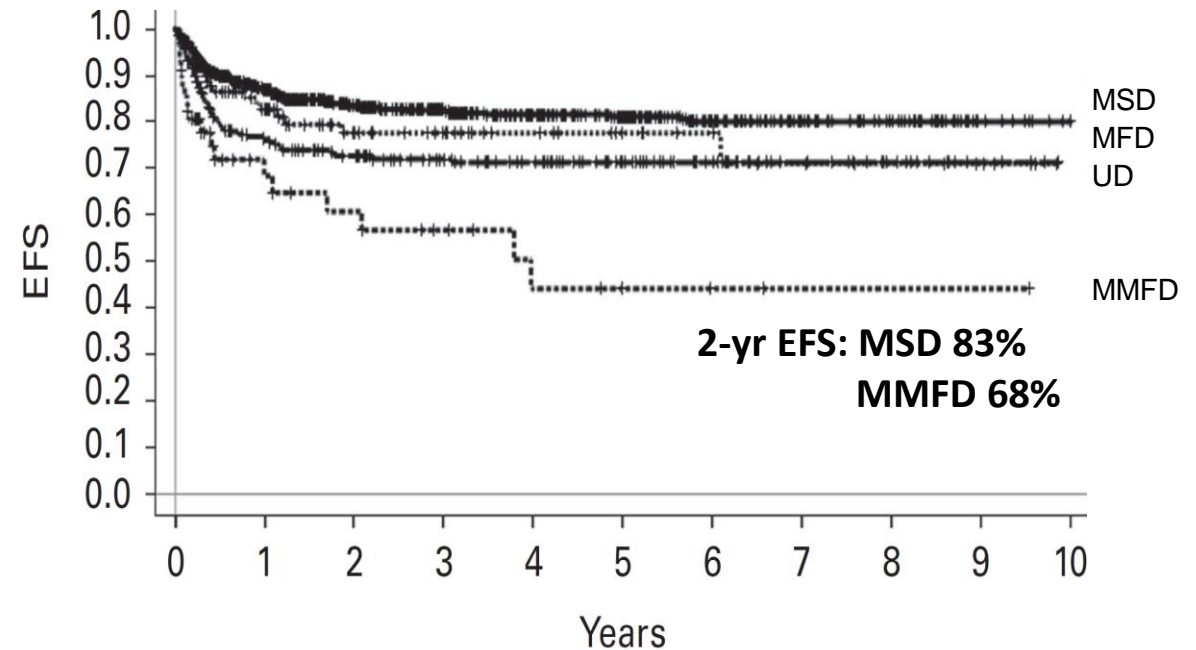
John E. J. Rasko, Alexis A. Thompson, Janet L. Kwiatkowski, Suradej Hongeng, Gary J. Schiller, Usanarat Anurathapan, P. Joy Ho, Manfred Schmidt, Morris Kletzel, Elliott Vichinsky, Briana Deary, Mohammed Asmal, Philippe Leboulch, Marina Cavazzana and Mark C. Walters

Transfusion-dependent β -thalassemia (TDT)

Iron overload in transfusion-dependent anemias¹



Event free survival in thalassemia patients following HSCT² (N=1455)



EFS, event free survival; HSCT, hematopoietic stem cell transplantation; LIC, liver iron concentration; MMFD, mismatched family donor; MSD, matched sibling donor

Northstar (HGB-204) study of LentiGlobin gene therapy in TDT

- LentiGlobin gene therapy contains autologous CD34+ HSCs transduced ex vivo with the BB305 lentiviral vector encoding β -globin with a T87Q amino acid substitution
- Northstar is an international, multi-center, Phase 1/2, open-label, single-arm study in adolescents/adults with TDT
 - Primary objectives: Safety and efficacy of LentiGlobin gene therapy in TDT

All 18 patients have completed the 2-year study

Median follow-up: 32.1 months
(min – max: 23.1 – 41.9 months)

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

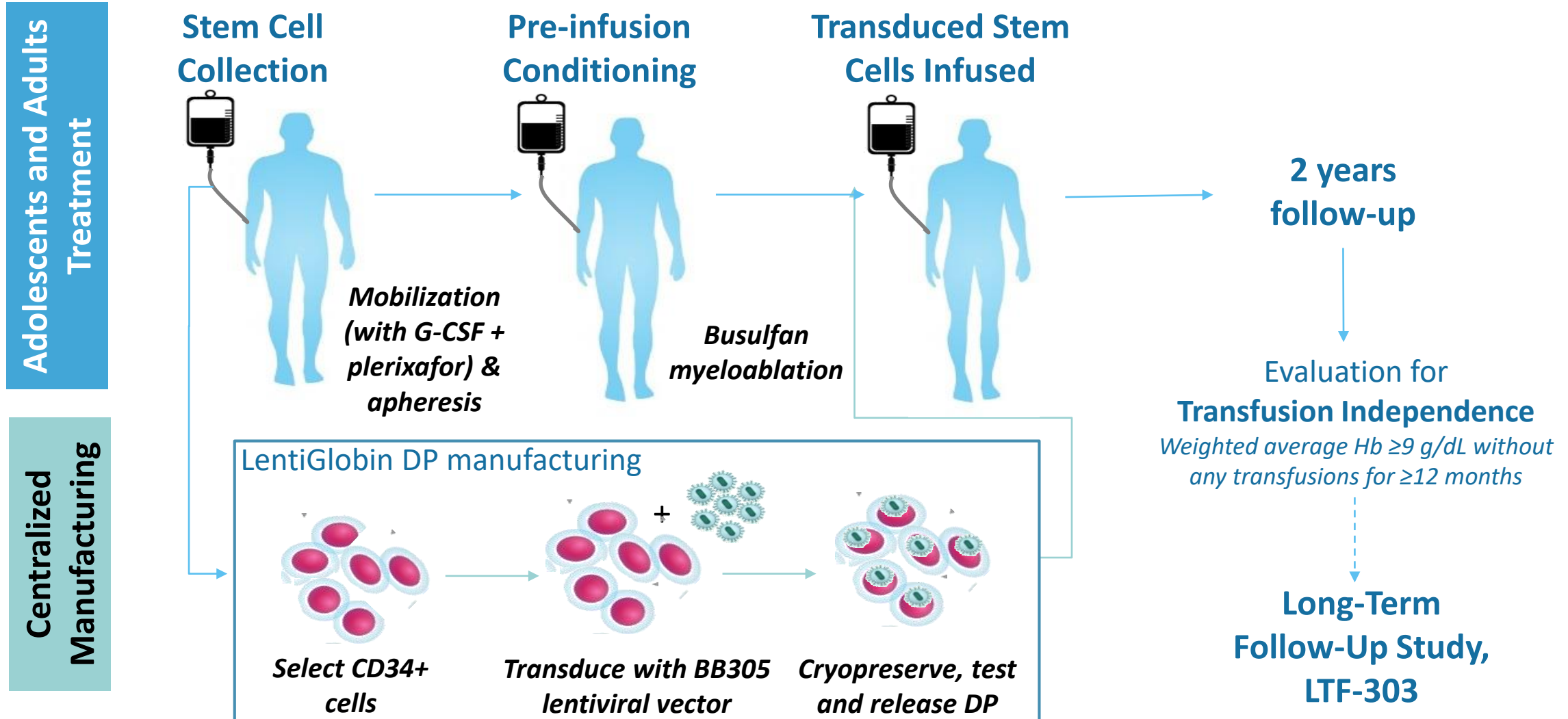


Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia

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

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

Overview of the Northstar (HGB-204) clinical study



DP, drug product; G-CSF, granulocyte-colony stimulating factor, Hb, hemoglobin

Patient and drug product characteristics

N=18 patients

Patient Characteristics		β^0/β^0 (n=8)	Non- β^0/β^0 (n=10)
Genotypes	β^E/β^0	—	6
	Other	—	4
Age at drug product infusion median (min – max), years		23.5 (13 – 36)	20.5 (16 – 35)
Pre-study pRBC transfusion volume annualized median (min – max), mL/kg/yr		182.7 (124.4– 261.3)	146.9 (139.1 – 234.5)
Liver Iron Concentration median (min – max), mg/g		6.3 (0.4 – 17.0)	5.7 (1.2 – 26.4)
Splenectomy n, %		3 (38)	3 (30)

Drug Product Characteristics	β^0/β^0 (n=8)	Non- β^0/β^0 (n=10)
	median (min – max)	
Busulfan AUC* $\mu\text{M}^*\text{min}$	4127 (3072 – 4714)	4060 (3030 – 4417)
Drug product VCN[†] vector copies/diploid genome	0.6 (0.3 – 1.5)	0.7 (0.3 – 1.1)
CD34+ cells transduced[†] %	32 (18 – 58)	29 (17 – 44)
Drug product cell dose CD34+ cells $\times 10^6/\text{kg}$	11.0 (6.1 – 18.1)	7.1 (5.2 – 13.0)

*Estimated average daily busulfan exposure over 4 days

†22 drug product lots manufactured for 18 patients

AUC, area under the curve; pRBC, packed red blood cells; VCN, vector copy number

Neutrophil and platelet engraftment

	Patients (N=18)
Neutrophil engraftment* median (min – max), study day	18.5 (14 – 30)
Platelet engraftment† median (min – max), study day	39.5 (19 – 191)

*Absolute neutrophil count \geq 500 cells/ μ L for 3 consecutive days

†Unsupported platelet count \geq 20,000 platelets/ μ L

- Cumulative incidence of neutrophil engraftment was 100% by Day +30
- Cumulative incidence of platelet engraftment was 78% by Day +60 and 94% by Day +100
- Median duration of hospitalization from conditioning to post-DP infusion discharge was 40 (min – max: 27 – 69) days

Safety of LentiGlobin treatment in adults and adolescents with TDT remains consistent with myeloablative conditioning

Non-hematologic* grade $\geq 3^{\dagger}$ 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)

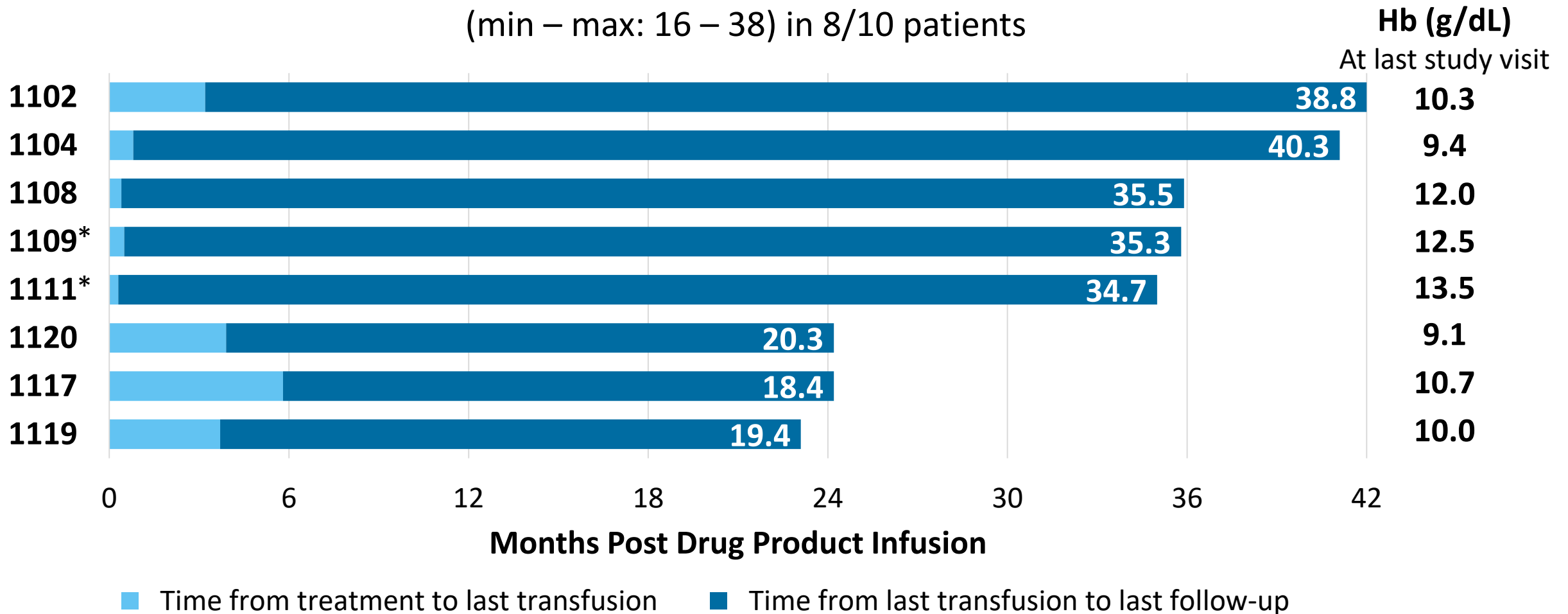
*Hematologic AEs commonly observed post-transplant have been excluded; [†]No grade 4 or 5 non-hematologic events were reported; [‡] Both VODs were grade 3 and serious events [§]Included 1 vena cava thrombosis and 1 intracardiac thrombus

- 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
- No evidence of clonal dominance

8/10 patients with non- β^0/β^0 genotypes achieved and maintain transfusion independence

Median duration of transfusion independence to date of 33 months
(min – max: 16 – 38) in 8/10 patients

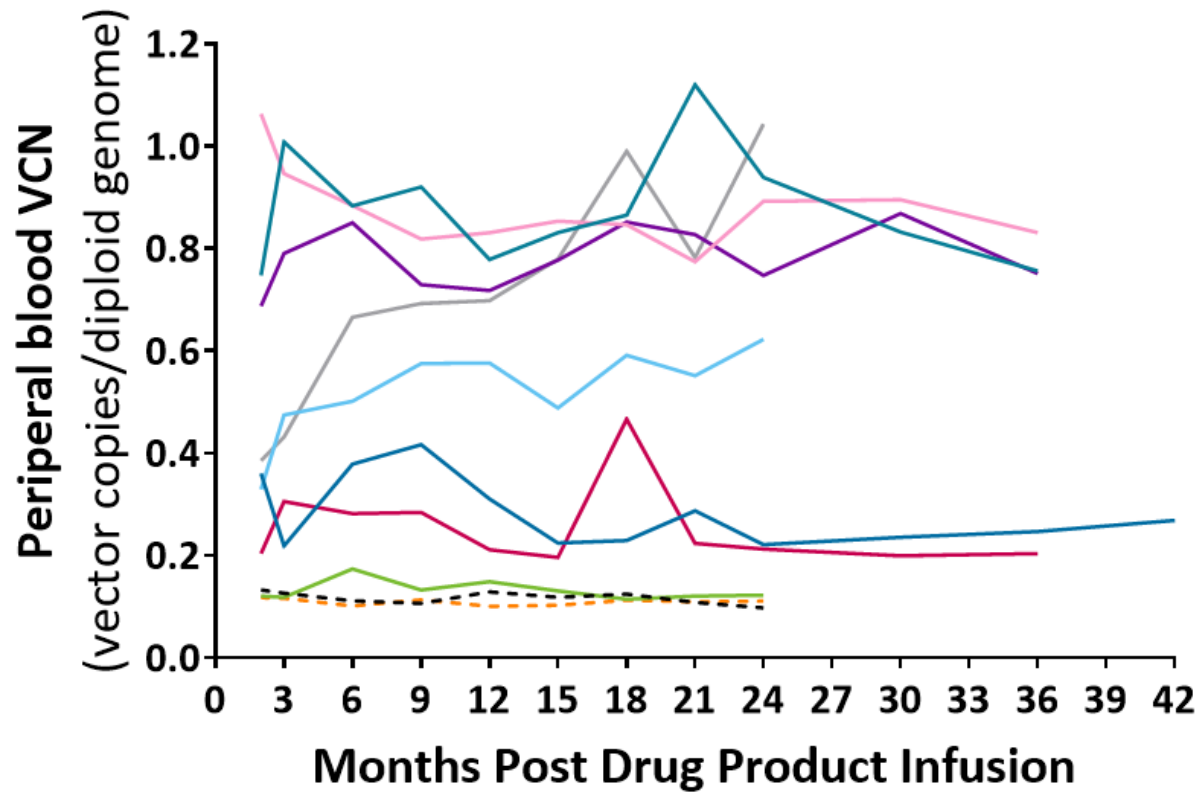


*Indicates male patients. Transfusion independence is defined as weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months. Hb, hemoglobin

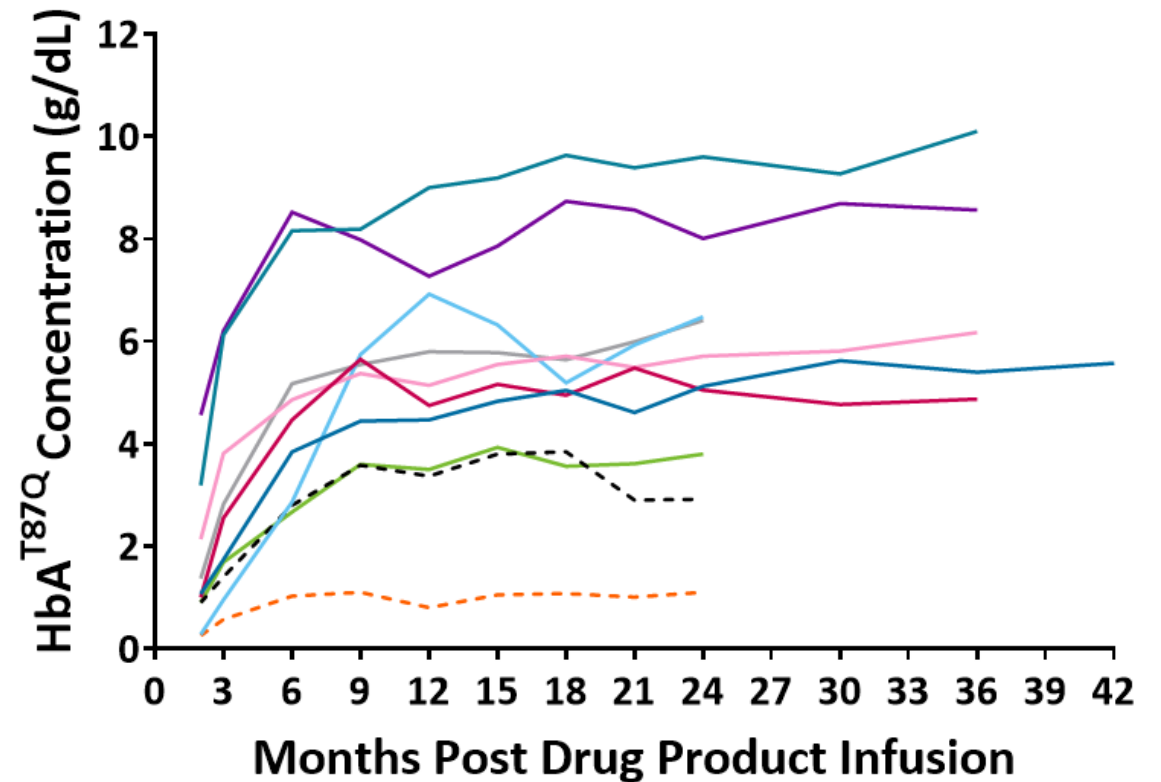
Peripheral VCN and HbA^{T87Q} production

Patients with non-β⁰/β⁰ genotypes

VCN in peripheral blood over time



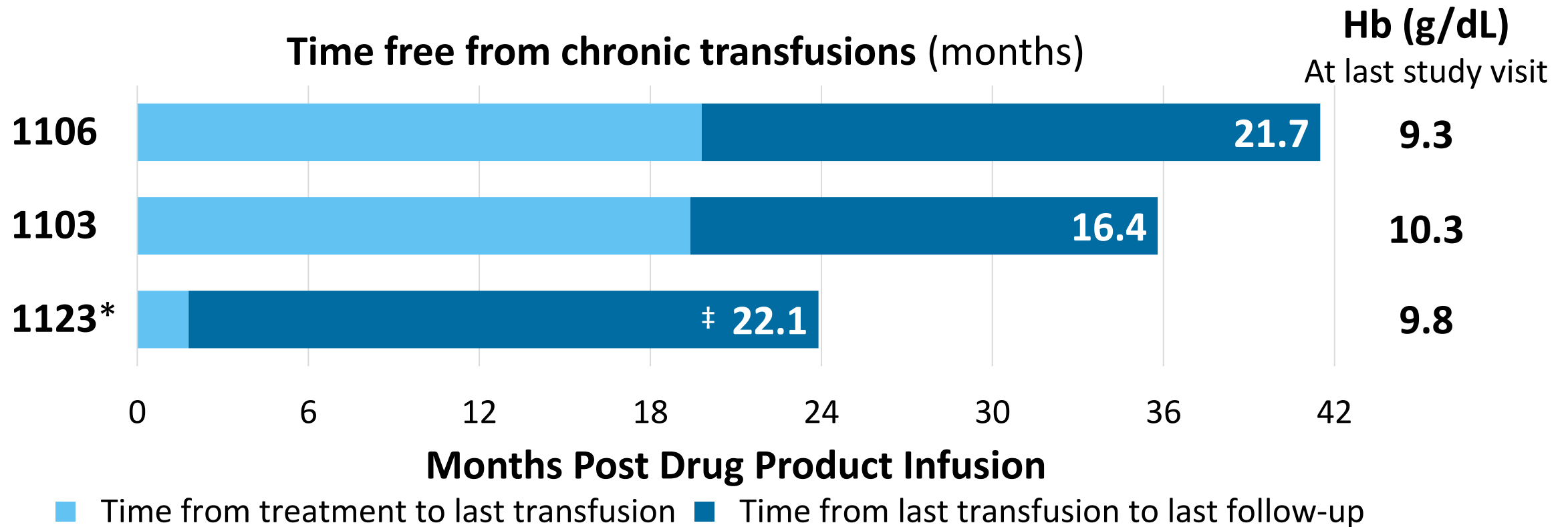
Gene therapy-derived hemoglobin (HbA^{T87Q}) over time



Dotted lines indicate patients receiving chronic transfusions

HbA^{T87Q}, Gene therapy-derived hemoglobin; VCN, vector copy number (vector copies/diploid genome)

3/8 patients with β^0/β^0 genotypes are free from chronic transfusions



Patients 1103 and 1123 achieved transfusion independence with a duration to date of 14 and 16 months, respectively

* Indicates male patient

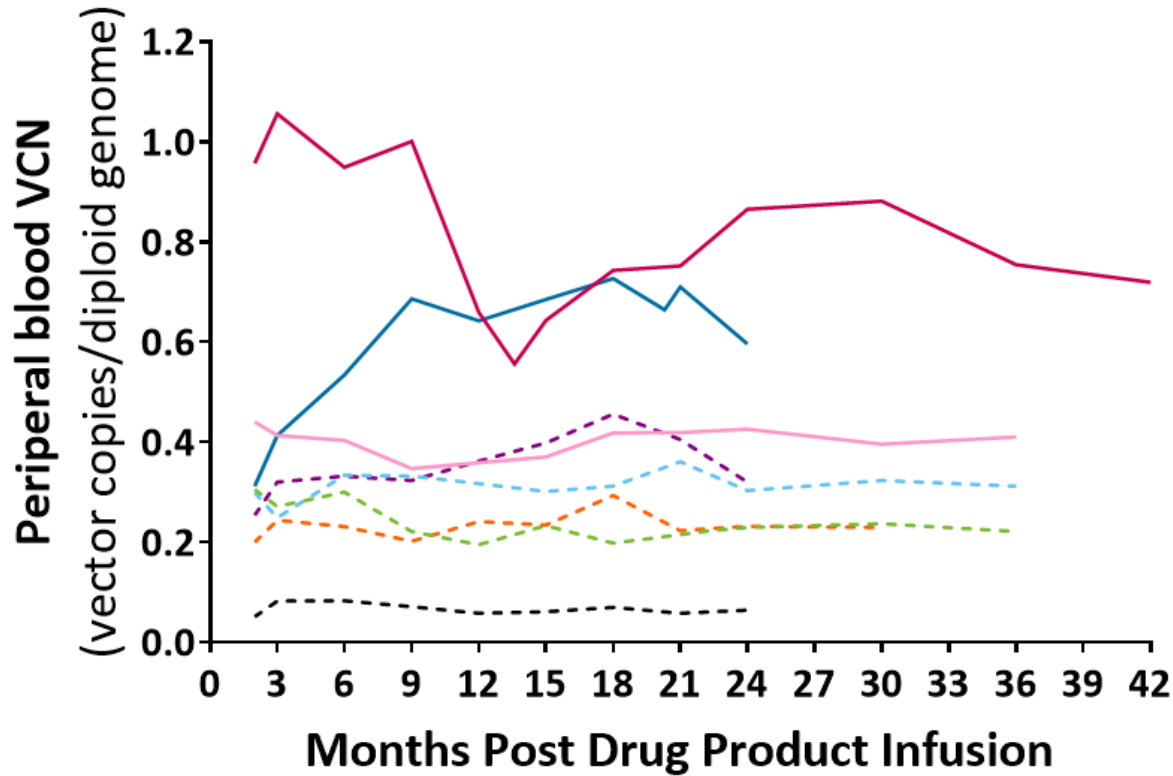
‡ Patient had a single transfusion for an acute event of cat scratch disease

Transfusion independence is defined as weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months. Hb, hemoglobin

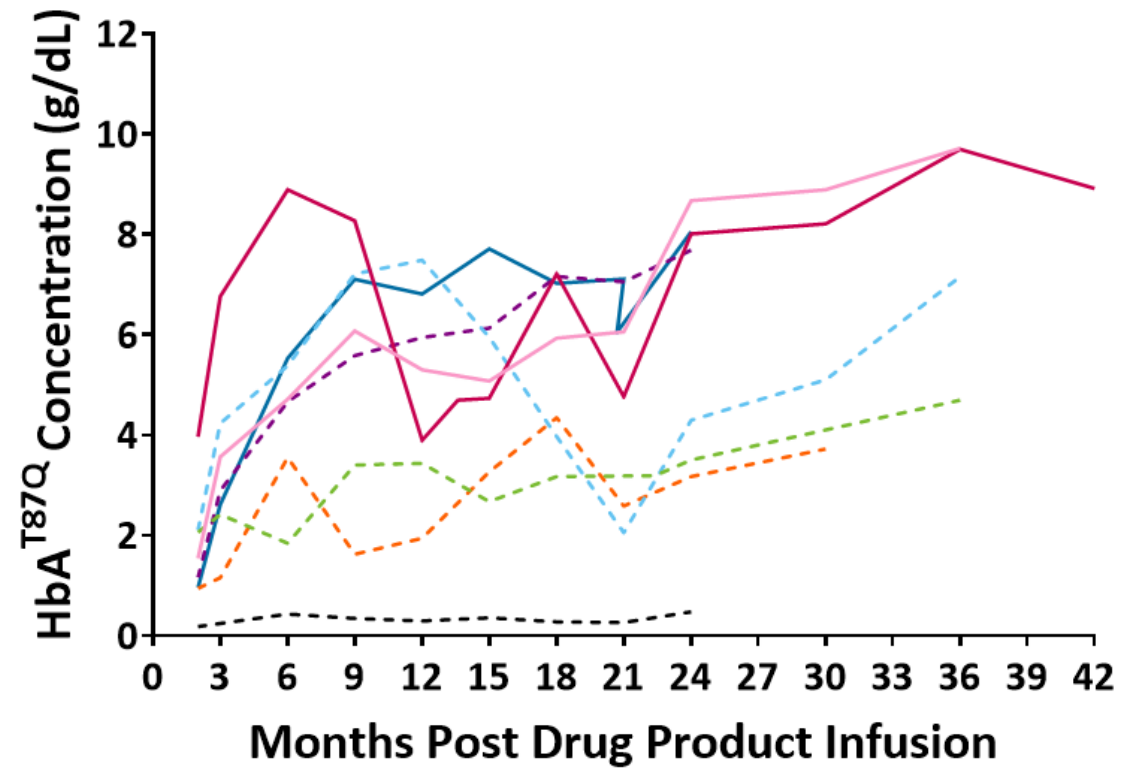
Peripheral VCN and HbA^{T87Q} production

Patients with β^0/β^0 genotypes

VCN in peripheral blood over time



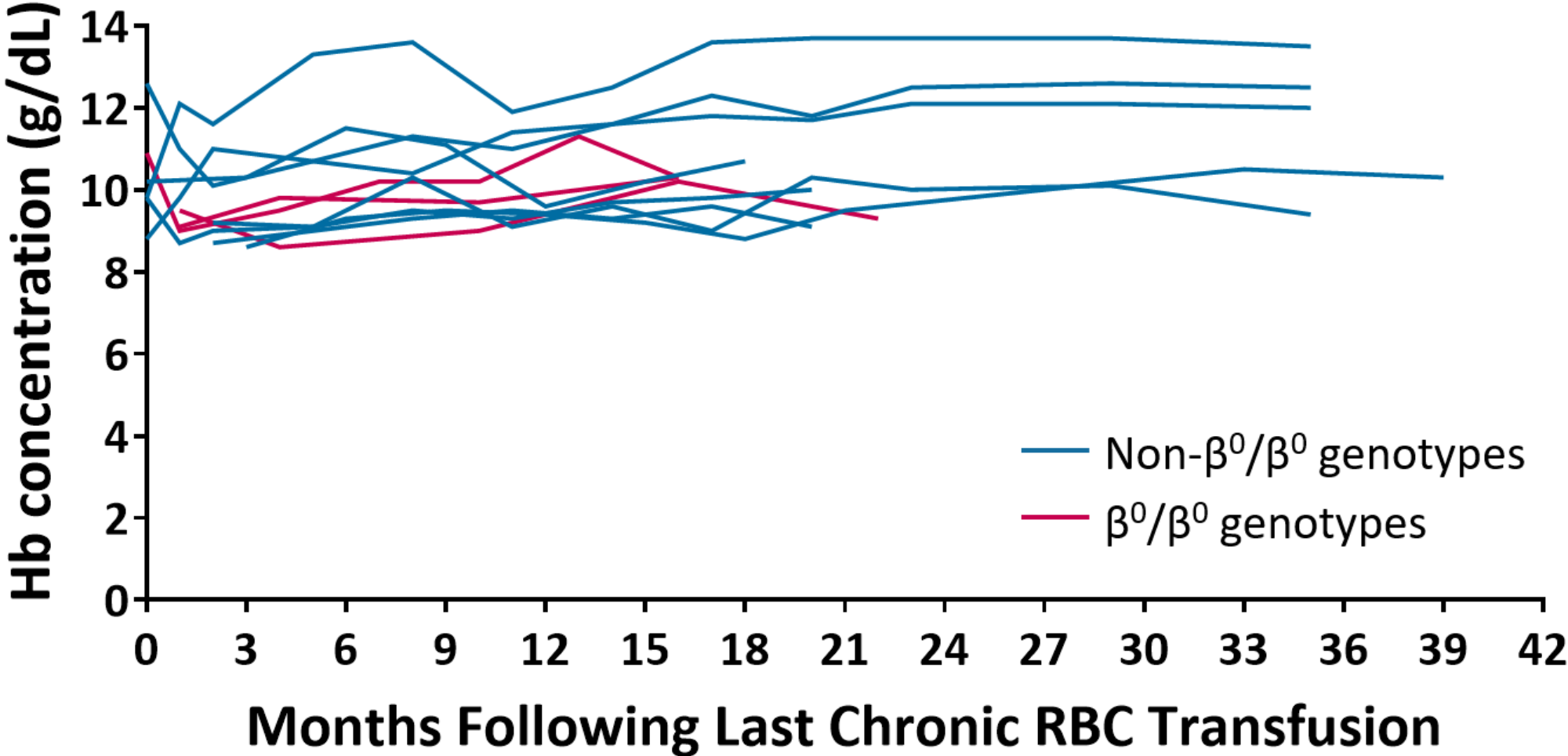
Gene therapy-derived hemoglobin (HbA^{T87Q}) over time



Dotted lines indicate patients receiving chronic transfusions

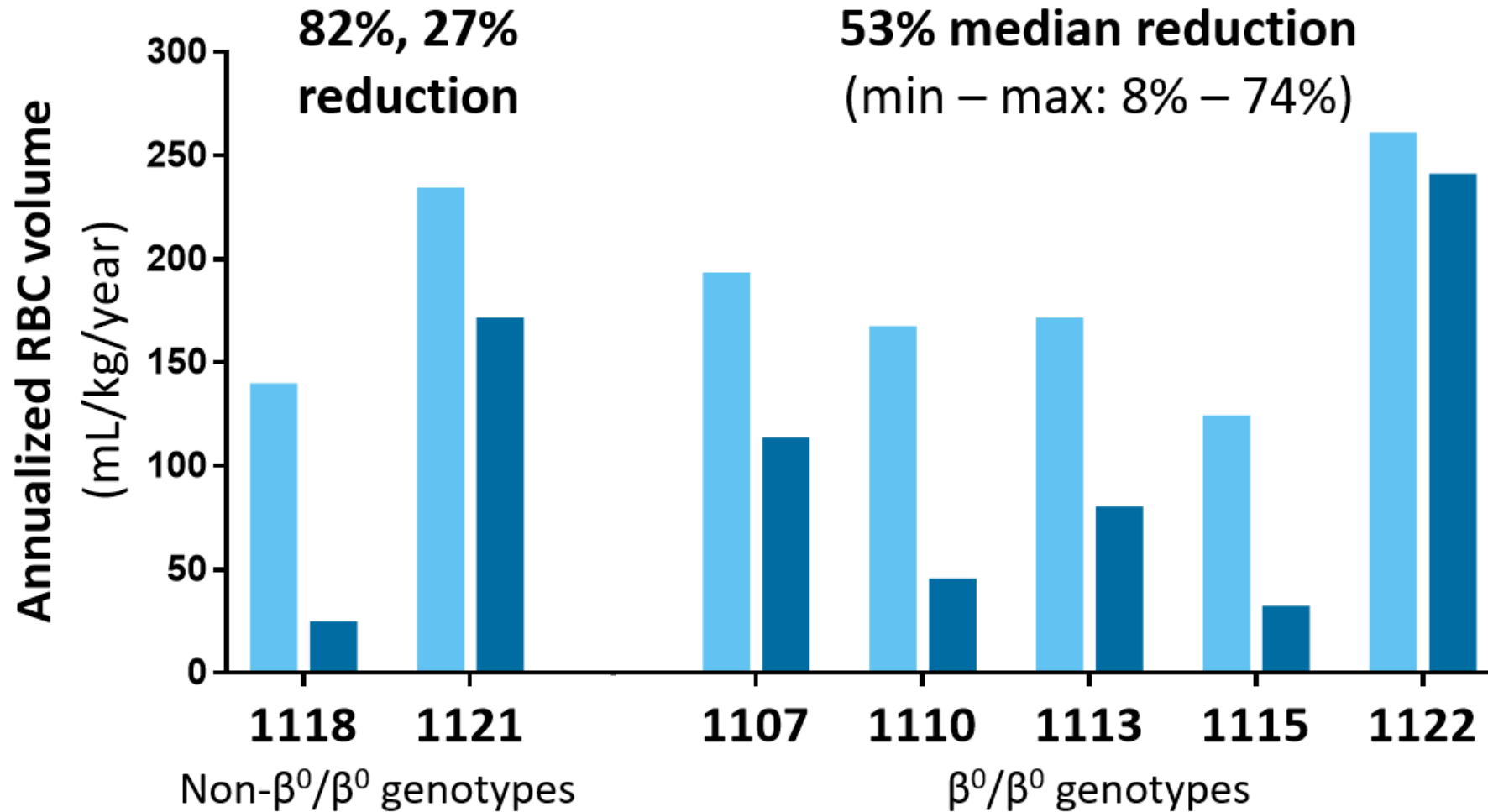
HbA^{T87Q}, Gene therapy-derived hemoglobin; VCN, vector copy number (vector copies/diploid genome)

Total hemoglobin remains stable following cessation of chronic transfusions



Hb, hemoglobin; RBC, red blood cell

Reduction in RBC transfusion volume in patients still receiving transfusions



82%, 27%
reduction

53% median reduction
(min – max: 8% – 74%)

Annualized RBC volume
(mL/kg/year)

1118

1121

1107

1110

1113

1115

1122

Non- β^0/β^0 genotypes

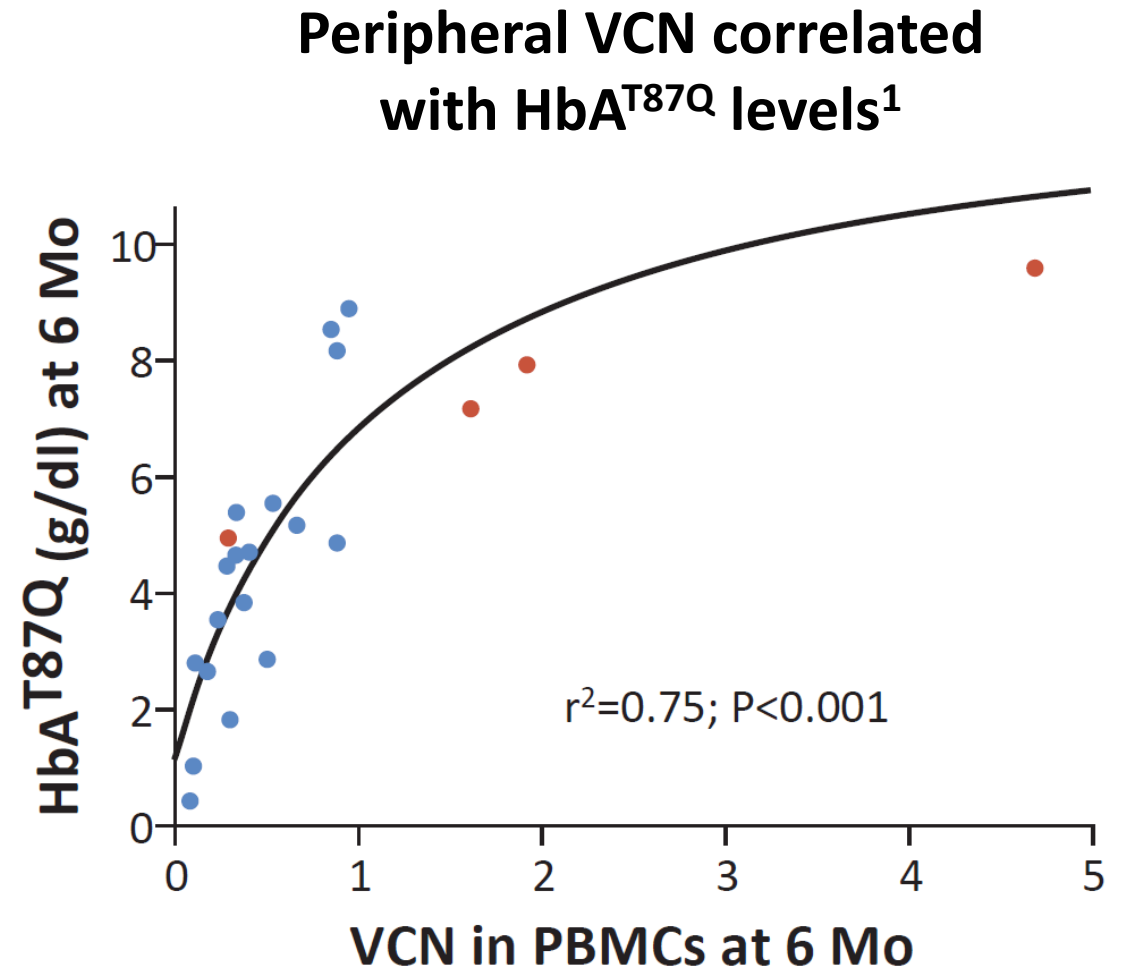
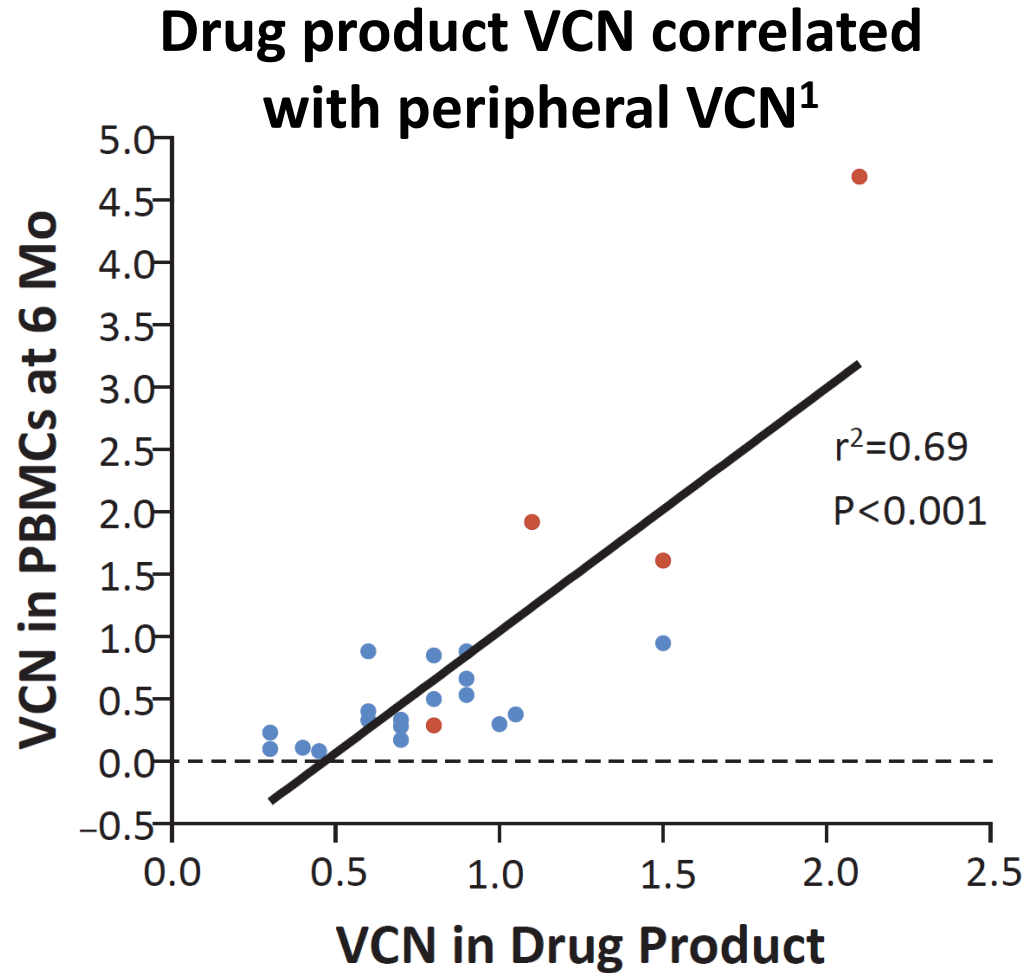
β^0/β^0 genotypes

Pre-treatment: Annualized volume of RBC transfusions in the 2 years prior to study enrollment

Post-treatment: Annualized on-study volume of RBC transfusions starting at month 6 post-DP infusion through last study visit

RBC, red blood cell

Peripheral VCN correlates with DP VCN and HbA^{T87Q} at Month 6



● HGB-204 ● HGB-205 (NCT02151526)

PBMC, peripheral blood mononuclear cells; VCN, vector copy number (vector copies/diploid genome)

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

Next steps: Pivotal phase 3 clinical studies of LentiGlobin in TDT

NORTHSTAR-2
STUDY

HGB-207

**Phase 3, multi-center, global study
NCT02906202**

- Non- β^0/β^0 genotypes
- N = 23 patients \leq 50 years of age
- Open and enrolling

NORTHSTAR-3
STUDY

HGB-212

**Phase 3, multi-center, global study
NCT03207009**

- β^0/β^0 genotypes
- N = 15 patients \leq 50 years of age
- Open and enrolling

Summary

- With up to 3.5 years of follow-up, LentiGlobin gene therapy has eliminated or reduced chronic RBC transfusions in most patients with TDT
 - 8/10 patients with non- β^0/β^0 genotypes and 3/8 patients with β^0/β^0 genotypes remain free from chronic transfusions
- Hemoglobin levels are stable at near-normal levels (9.1 – 13.5 g/dL) in transfusion-free patients
- Safety profile is consistent with myeloablative conditioning with busulfan
 - No grade ≥ 3 AEs were considered related to LentiGlobin
- Two phase 3 studies are underway to evaluate LentiGlobin safety and efficacy in TDT using a refined DP manufacturing process:
 - Northstar-2 (non- β^0/β^0 genotypes)
 - Northstar-3 (β^0/β^0 genotypes)

Thank you to the study participants and their families

UCSF Benioff Children's Hospital

- Mark Walters
- Elliott Vichinsky
- Cyrus Bascon
- Ash Lal
- Marci Moriarty

University of California, Los Angeles

- Gary J. Schiller

bluebird bio. Inc

- Mohammed Asmal
- Alexandria Petrusich
- Briana Deary
- Ying Chen
- Sarah Hunter
- Kimberly Price

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

- Alexis Thompson
- Morris Kletzel
- Katherine Hammond

Children's Hospital of Philadelphia

- Janet Kwiatkowski
- David Teachey
- Isaiah Sommers

GeneWerk GmbH

- Manfred Schmidt

Hôpital Necker-Enfants Malades, IMAGINE Institute, Groupe Hôpitalier Universitaire Paris Ouest

- Marina Cavazzana

Ramathibodi Hospital, Mahidol University

- Suradej Hongeng
- Usanarat Anurathapan
- Philippe Leboulch
- Kesinee Jongrak

Royal Prince Alfred Hospital, Sydney Medical School

- John E. J. Rasko
- P. Joy Ho
- Samuel Gardiner
- Divya Suthat