

Clinical Outcomes of LentiGlobin Gene Therapy for Transfusion-Dependent β -Thalassemia Following Completion of the Northstar (HGB-204) Study

Mark C. Walters, Janet L. Kwiatkowski, John E.J. Rasko, Suradej Hongeng, Gary J. Schiller, Usanarat Anurathapan, Marina Cavazzana, P. Joy Ho, Manfred Schmidt, Morris Kletzel, Elliott Vichinsky, Briana Deary, Ying Chen, Alexandria Petrusich, Alexis A. Thompson

DISCLOSURE OF AFFILIATIONS

M. Walters

Disclosures

- Bluebird Bio: Research Funding
- Sangamo Therapeutics: Consultancy
- AllCells Inc.: Medical Director
- ViaCord Processing Lab: Medical Director

Northstar (HGB-204) study

Phase 1/2 study of autologous CD34+ cells encoding β^{A-T87Q} -globin gene (LentiGlobin for β -thalassemia)

Key eligibility criteria

- Transfusion-dependent β -thalassemia
- Non- β^0/β^0 genotype or β^0/β^0 genotype
- 12 – 35 years of age

Primary efficacy outcomes:

- ≥ 2 g/dL HbA^{T87Q} 18 – 24 months post-infusion
- Transfusion Independence
 - Weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months

Study Status

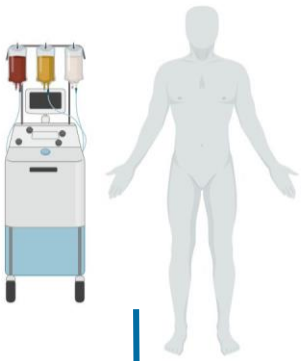
- All 18 patients have completed the 2-year study and enrolled in long-term follow-up study, LTF-303
- **Median follow-up: 40.7 months** (min – max: 29.3 – 53.8 months)

RBC, red blood cells

HGB-204: Study design

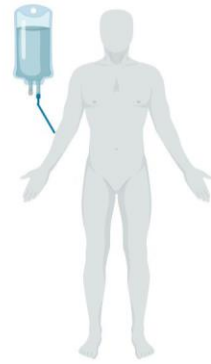
HSC collection

*Mobilization
(G-CSF + plerixafor) &
apheresis*

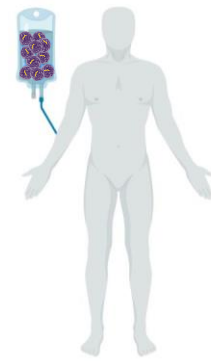


Busulfan

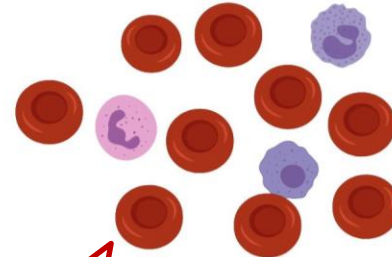
**myeloablative
conditioning**



DP infusion



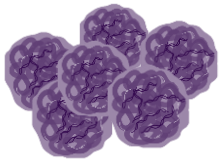
**Transduced HSCs engraft and
reconstitute functional RBCs**



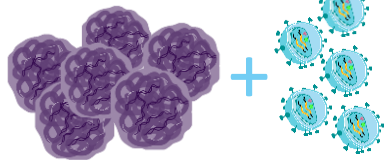
**2-yr
Follow-up**

**Long-Term
Follow-Up Study**

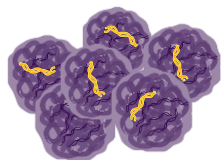
LentiGlobin centralized manufacturing



**Select
CD34+ cells**



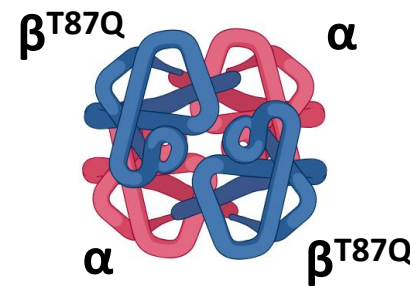
**Transduce with BB305
lentiviral vector**



**Cryopreserve,
test, release DP**

Gene therapy-derived

HbA^{T87Q}



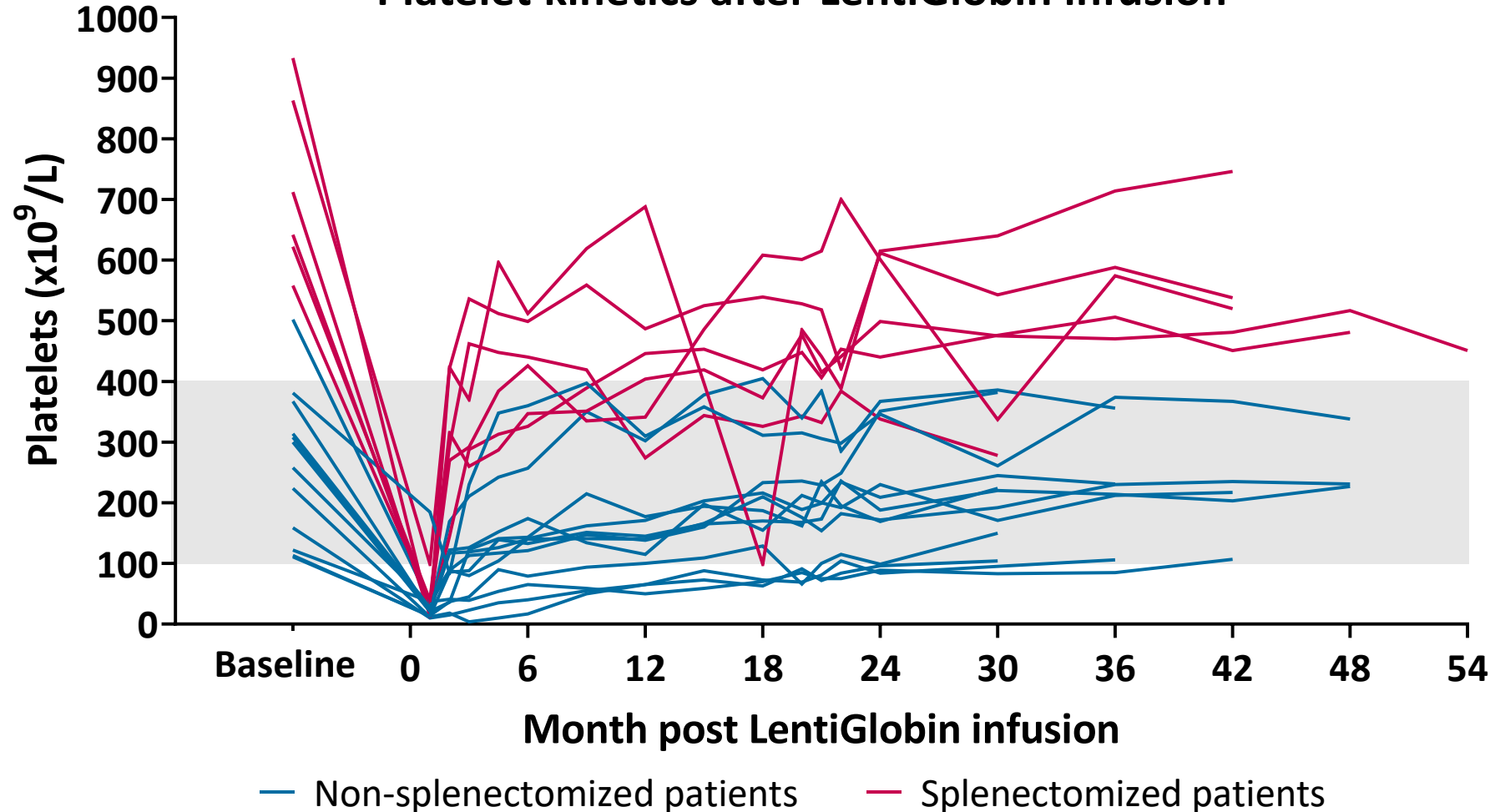
HGB-204: Patient and drug product characteristics

Patient Characteristics		N = 18
Genotypes	β^0/β^0	8
	β^E/β^0	6
	Other	4
Age at consent		20
	median (min – max), yrs	(12 – 35)
Pre-study RBC transfusion volume		169
	annualized median (min – max), mL/kg/yr	(124 – 273)
Liver iron concentration		5.7
	median (min – max), mg Fe/g dw	(0.4 – 26.4)

Drug Product Characteristics <i>per patient</i>		N = 18 median (min – max)
Drug product cell dose		8.1
	$\times 10^6$ CD34+ cells/kg	(5.2 – 18.1)
Drug product VCN		0.7
	vector copies/diploid genome	(0.3 – 1.5)
CD34+ cells transduced		31.5
	%	(17 – 58)
Treatment Characteristics		
Neutrophil engraftment		18.5
	ANC \geq 500 cells/ μ L x 3 days, days	(14 – 30)
Platelet engraftment		39.5
	Platelets \geq 20k/ μ L, days	(19 – 191)

HGB-204: Platelet recovery to normal range without excess bleeding complications

Platelet kinetics after LentiGlobin infusion



Bleeding AEs

- Grade ≥ 3 bleeding AEs from LentiGlobin infusion to platelet engraftment:
 - Epistaxis (Gr 3; n=2)
- No grade ≥ 3 bleeding AEs after platelet engraftment
- No serious bleeding events after LentiGlobin infusion

Gray bar indicates reference range. AE, adverse event; Gr, grade

HGB-204: Safety of LentiGlobin is generally consistent with myeloablative conditioning

Non-hematologic* grade $\geq 3^{\dagger}$ AEs reported in ≥ 2 patients	N = 18
<i>LentiGlobin infusion to 2 years follow-up</i>	n (%)
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	
<i>LentiGlobin infusion to last follow-up</i>	
Thrombosis [§]	2 (11)
Veno-occlusive liver disease [‡]	2 (11)

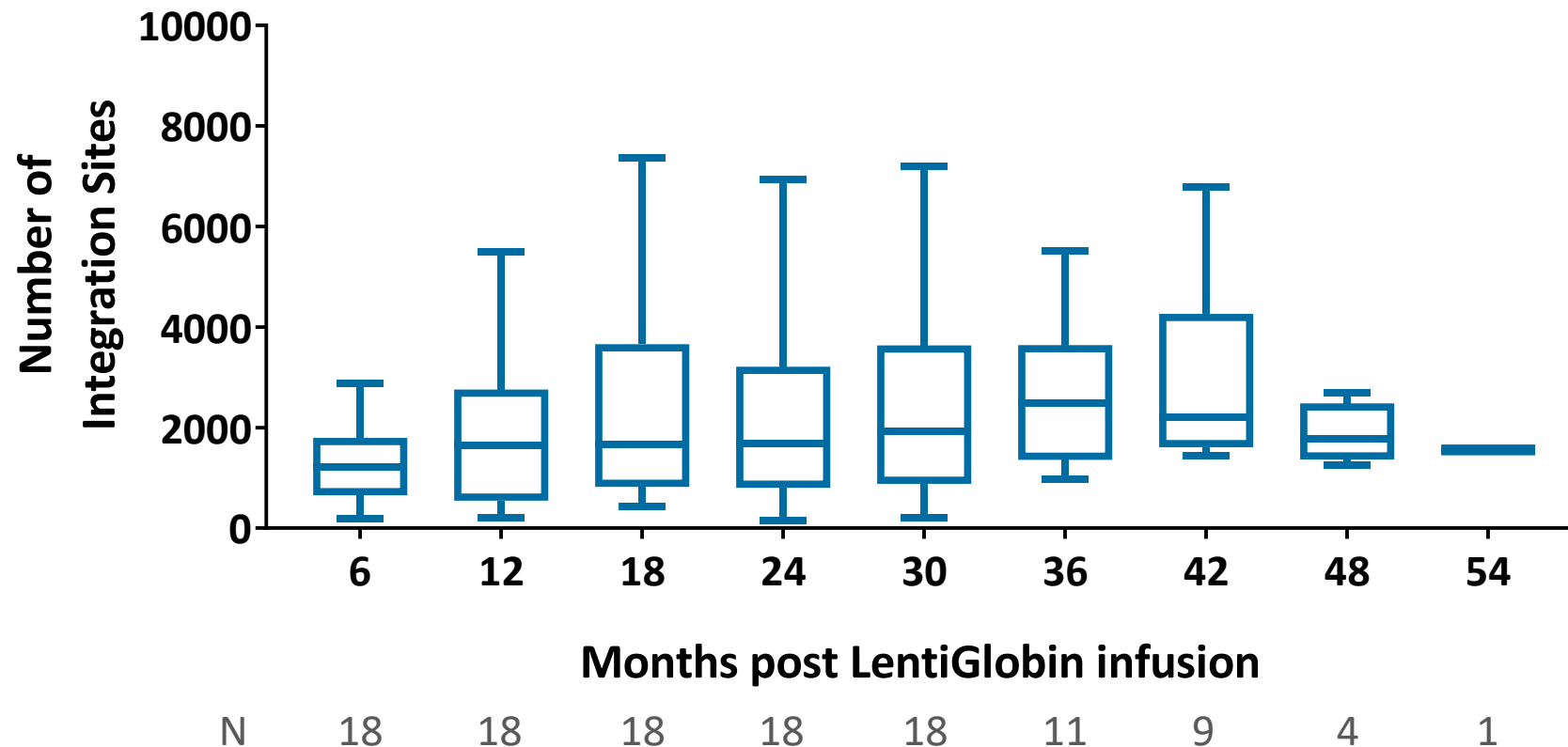
- No grade ≥ 3 DP-related AEs
- No deaths or graft failure
- No vector-mediated replication competent lentivirus

*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

HGB-204: Vector integration profile is polyclonal over time

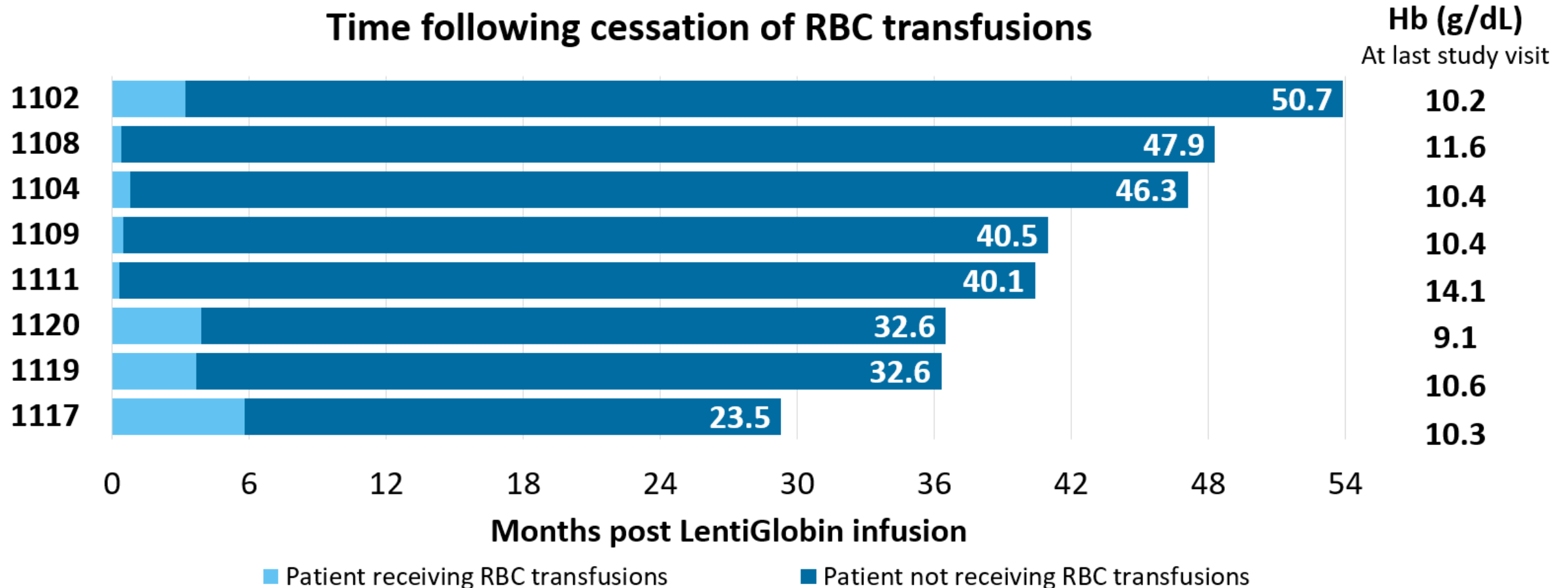
No clonal dominance has been observed

No single integration site contributed to more than 30% of all integration sites at any time



HGB-204: 8/10 patients with non- β^0/β^0 genotypes achieved and maintained transfusion independence

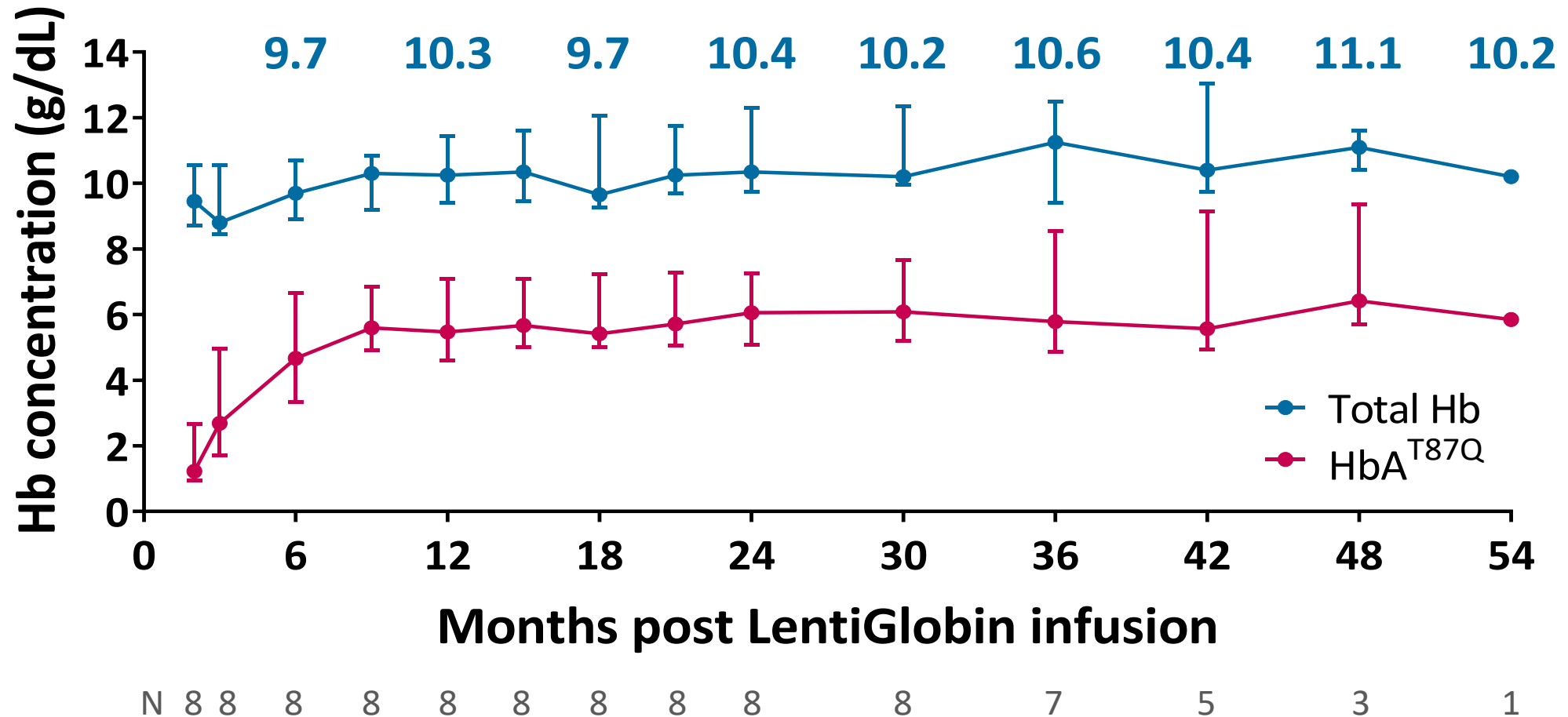
Time following cessation of RBC transfusions



Median duration of TI: 38.0 months (min – max: 21.2 – 45.3 months); responses are ongoing
Median weighted average Hb during TI: 10.3 g/dL (min – max: 9.3 – 13.2 g/dL)

HGB-204: HbA^{T87Q} expression is stable following LentiGlobin through 4 years and beyond

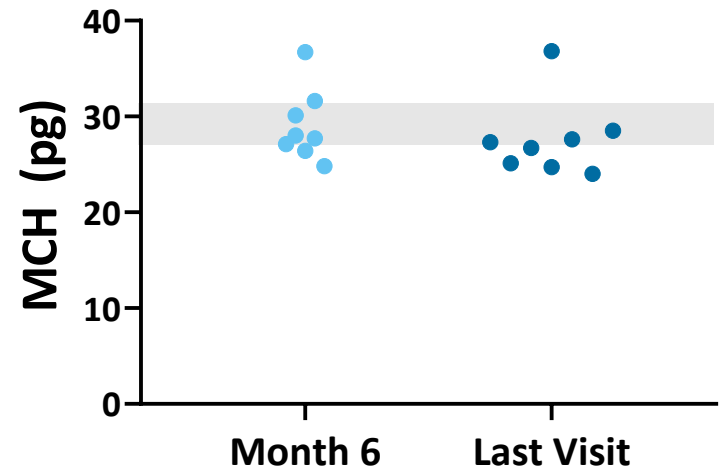
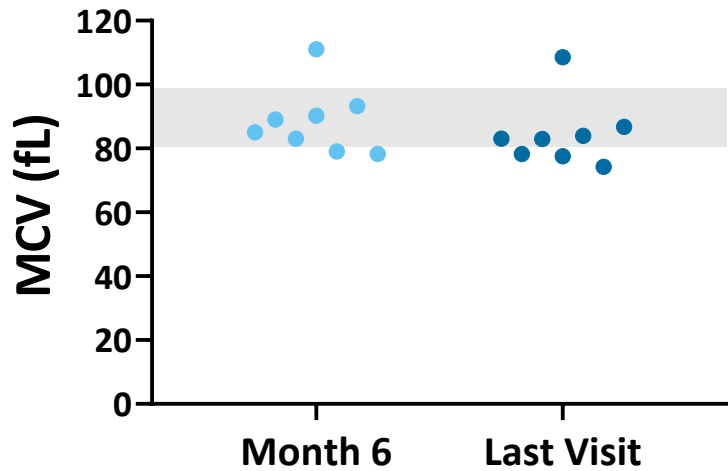
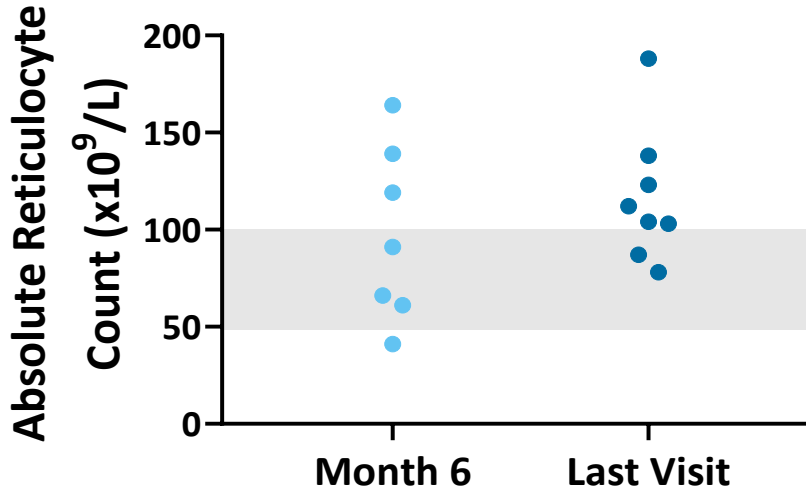
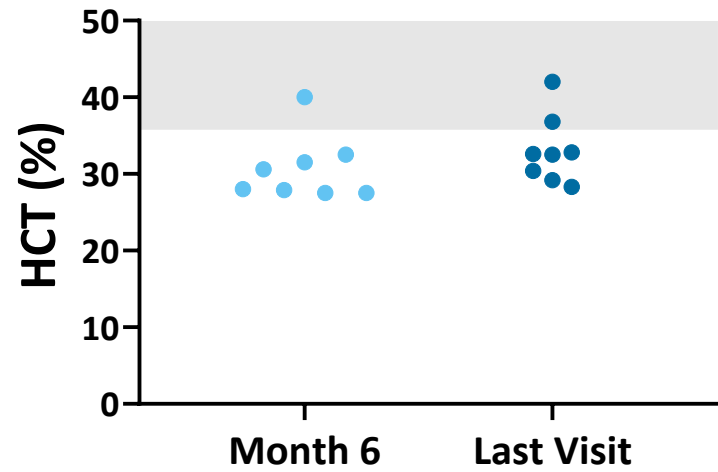
Median Hb in patients with non- β^0/β^0 genotypes who achieved transfusion independence



Medians (Q1, Q3) depicted; Hb, hemoglobin

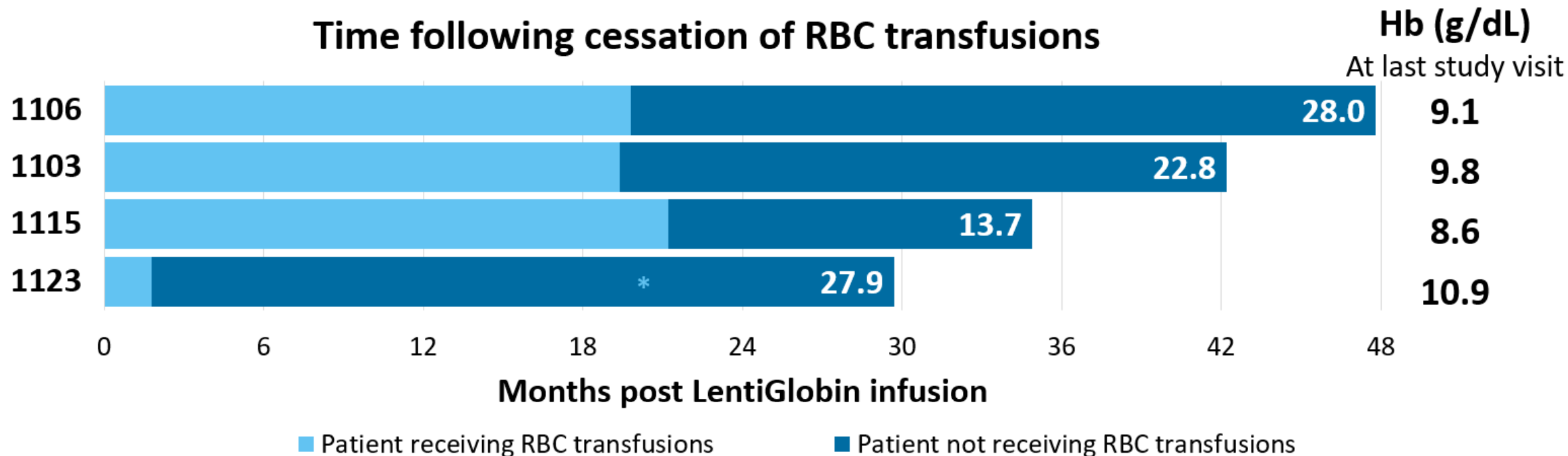
HGB-204: RBC indices were generally normal with transfusion independence

RBC indices in patients with non- β^0/β^0 genotypes who achieved transfusion independence



Last visit ranges from Month 36 to Month 54 post LentiGlobin infusion. Gray bar indicates reference range.

HGB-204: 4/8 patients with β^0/β^0 genotypes have been transfusion free for > 12 months



3/8 patients with β^0/β^0 genotypes have achieved transfusion independence

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

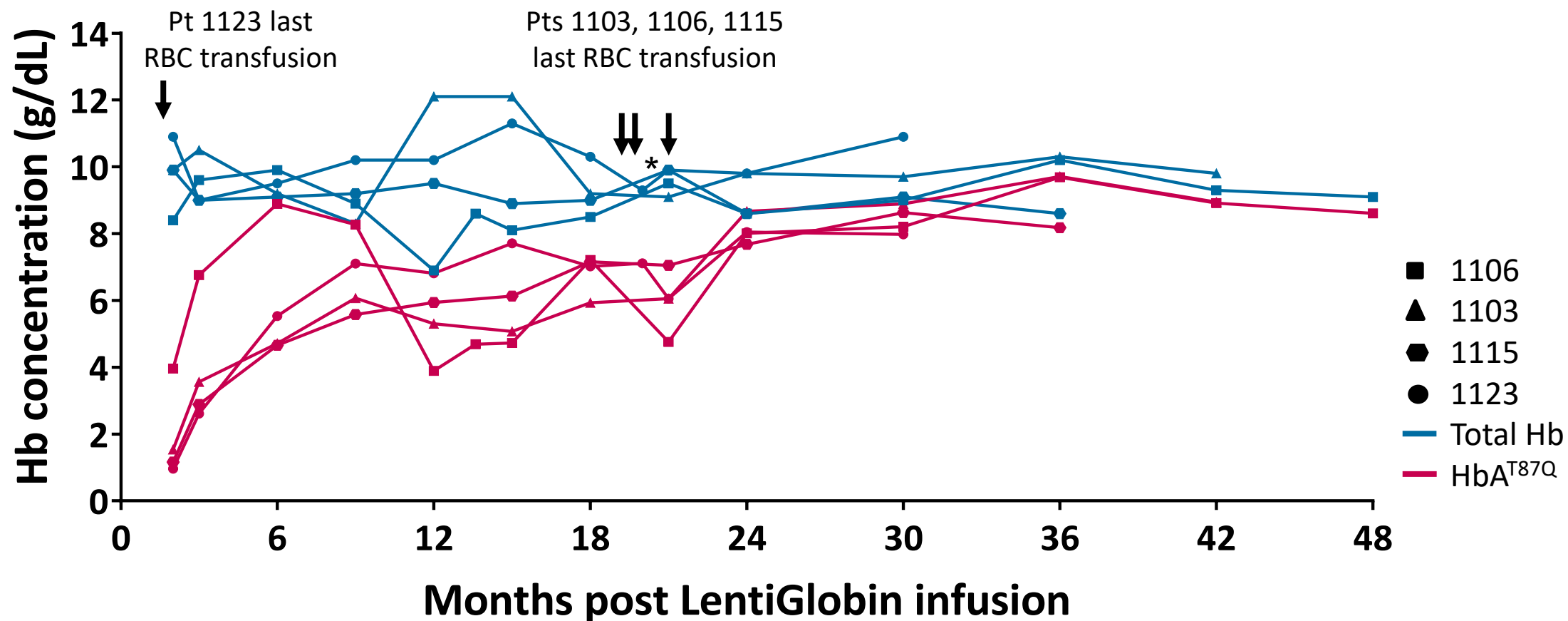
Median duration of TI: 16.4 months (min – max: 16.1 – 20.8 months)

Median weighted average Hb during TI: 9.9 g/dL (min – max: 9.5 – 10.1 g/dL)

*Patient had a single transfusion for an acute event of cat scratch disease. Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence

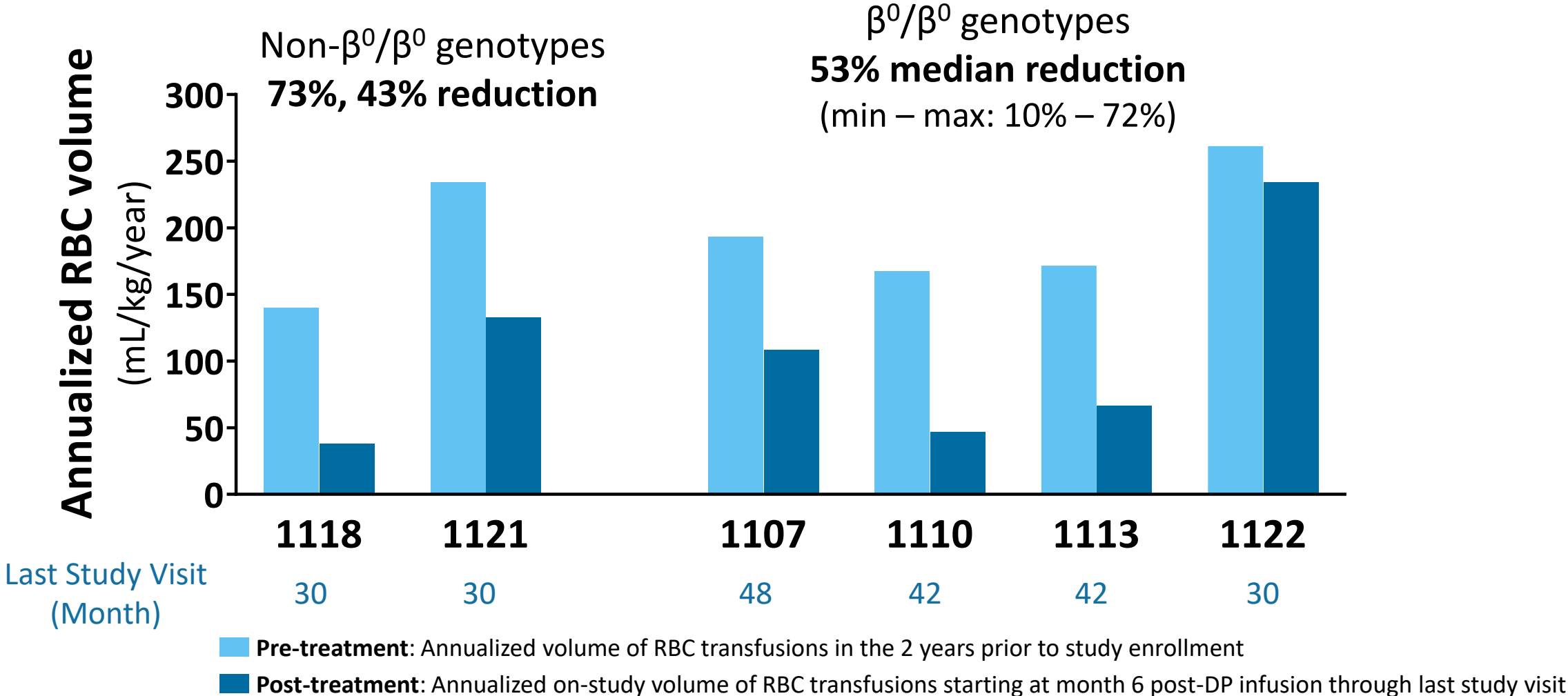
HGB-204: HbA^{T87Q} contributed to >90% total Hb in 3/4 patients with β^0/β^0 genotypes who are transfusion free

Hb in patients with β^0/β^0 genotypes who have been transfusion free for > 12 months



*Patient 1123 had a single transfusion for an acute event of cat scratch disease. Hb, hemoglobin; RBC, red blood cell

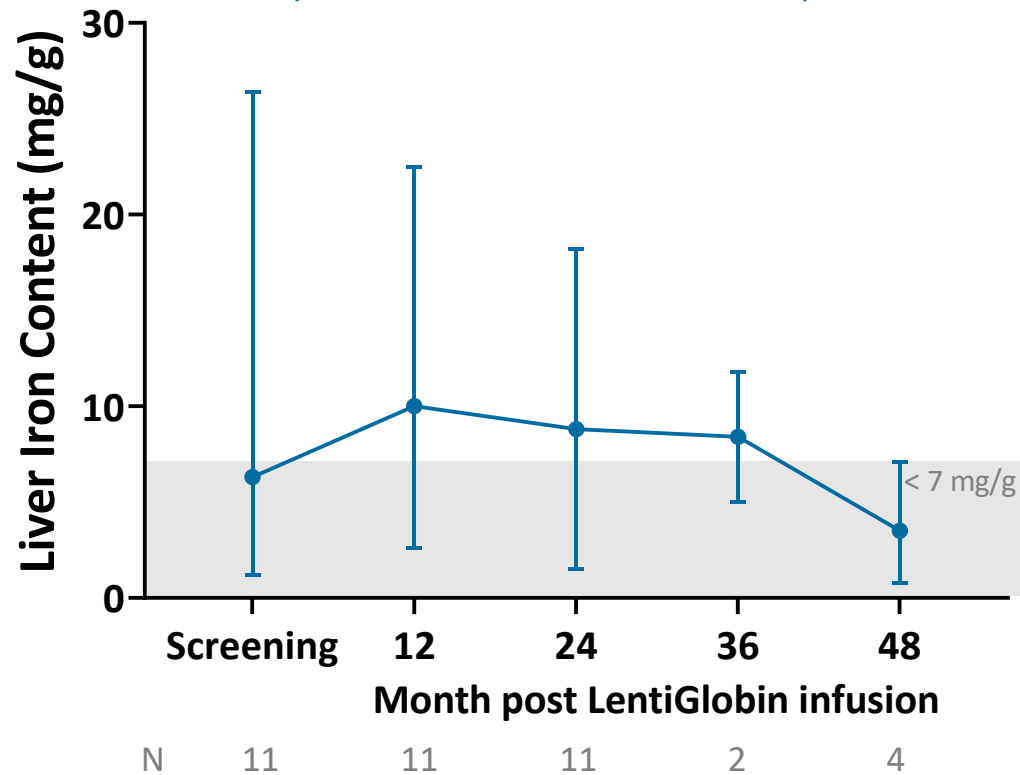
HGB-204: Reduction in RBC transfusion volume in patients still receiving transfusions



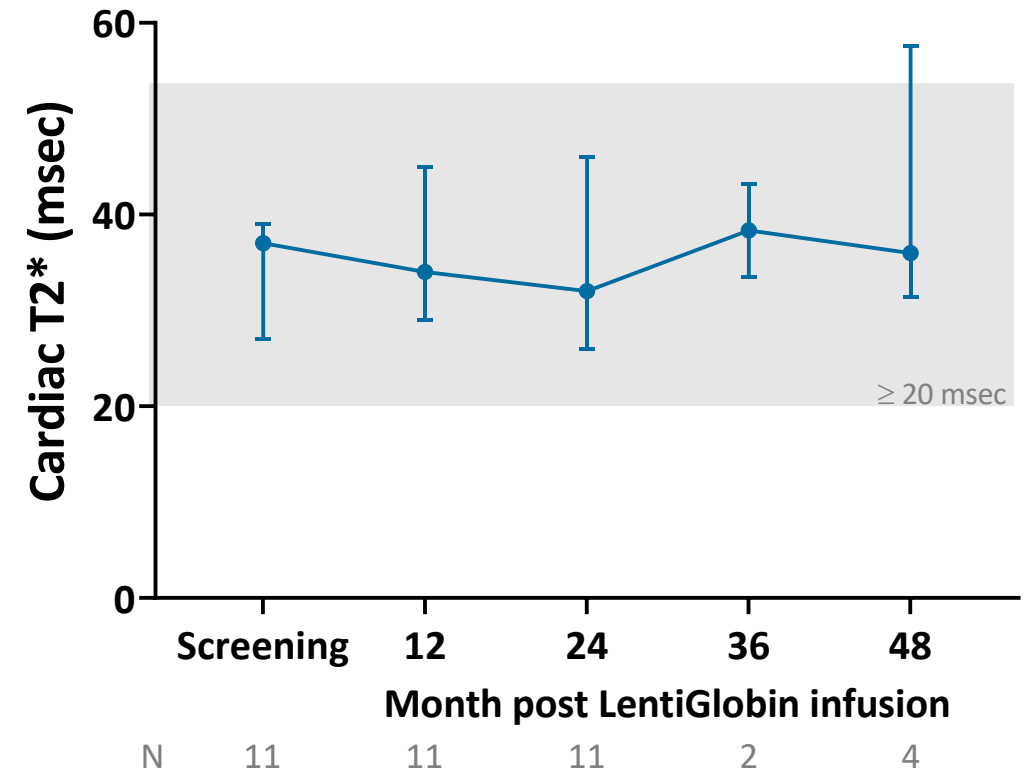
DP, drug product; RBC, red blood cell

HGB-204: Liver iron concentration decreased and cardiac T2* remained stable in patients who achieved transfusion independence

56% median reduction in LIC between baseline and M48
with re-initiation of iron chelation
(min – max: 38% – 83%; N = 4)



Cardiac T2* remained stable from screening to M48
Median increase 0.2%
(min – max: 17% reduction to 106% increase; N = 4)



Patients re-initiated iron chelation therapy a median of 13 months after LentiGlobin infusion (min – max: 2 – 15 months)

HGB-204: Summary

- Patients with TDT have been followed for up to 4.5 years after LentiGlobin gene therapy
- 80% (8/10) of patients with non- β^0/β^0 genotypes achieved durable transfusion independence (TI)
 - Total Hb was 9.1 – 14.1 g/dL at last visit; HbA^{T87Q} remains stable
- 38% (3/8) of patients with β^0/β^0 genotypes achieved TI
- In patients who achieved TI
 - RBC indices were generally within normal ranges
 - LIC decreased over time
- The safety profile of LentiGlobin is generally consistent with myeloablative conditioning
 - Some patients had delayed platelet engraftment, but no serious bleeding events

Thank you to the study participants and their families

UCSF Benioff Children's Hospital

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

University of California, Los Angeles

- Gary J. Schiller

bluebird bio. Inc

- Alexandria Petrusich
- Richard Colvin
- Briana Deary
- Kimberly Price
- Vanessa Lane
- Ying Chen
- Brooke Orr
- Joan Zape

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

- Alexis A. Thompson
- Morris Kletzel
- Katherine Hammond

Children's Hospital of Philadelphia

- Janet L. Kwiatkowski
- David Teachey
- Pranaya Venkatapuram

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
- Kesinee Jongrak

Royal Prince Alfred Hospital, Sydney Medical School

University of Sydney

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