

**Results from the phase 3 Northstar-3 study
evaluating LentiGlobin gene therapy in patients with
transfusion-dependent β -thalassemia and a β^0 or
IVS-I-110 mutation at both alleles of the *HBB* gene**

Andreas E. Kulozik, Franco Locatelli, Evangelia Yannaki, John B. Porter,
Isabelle Thuret, Martin G. Sauer, Ashutosh Lal, Janet L. Kwiatkowski,
Heidi Elliot, Ying Chen, Richard A. Colvin, Alexis A. Thompson

DISCLOSURE OF AFFILIATIONS

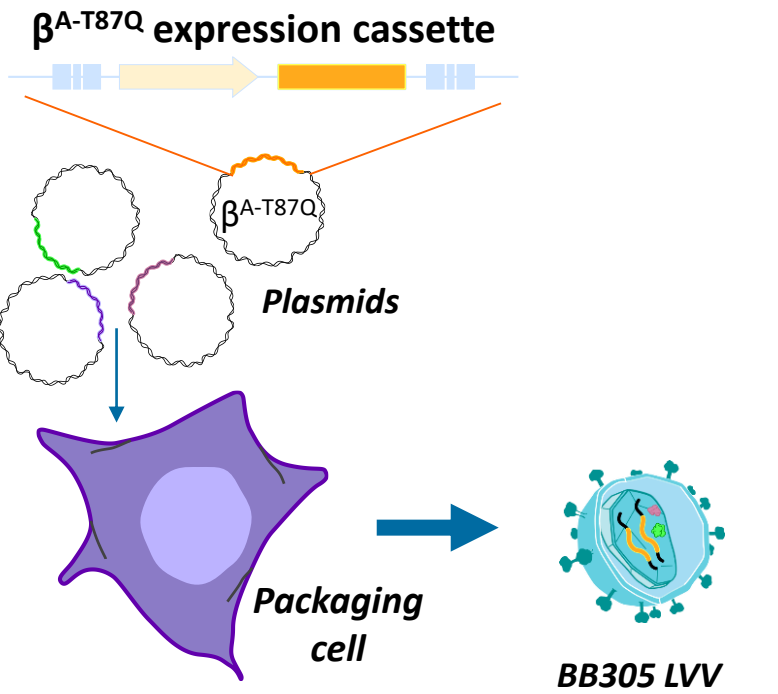
A. Kulozik

Disclosures

- Bluebird Bio: Consultancy and Honoraria

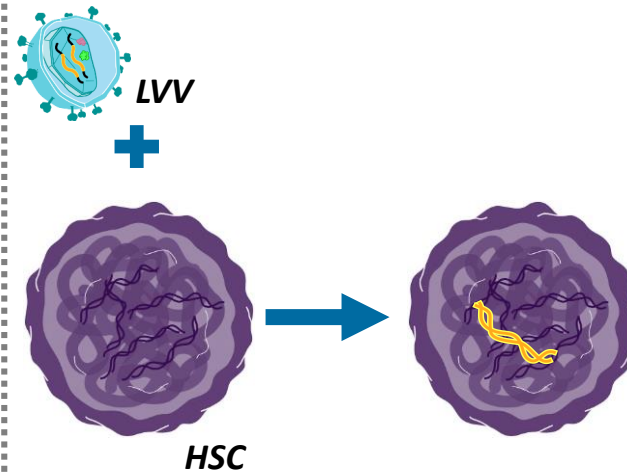
LentiGlobin *ex vivo* gene addition therapy

BB305 lentiviral vector production

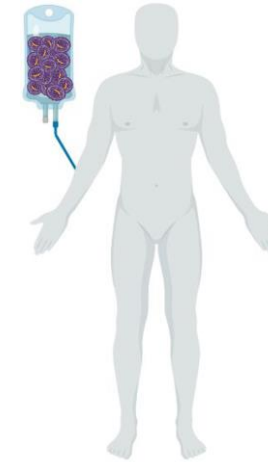


Only select HIV genes required for certain functions are used to make LVVs

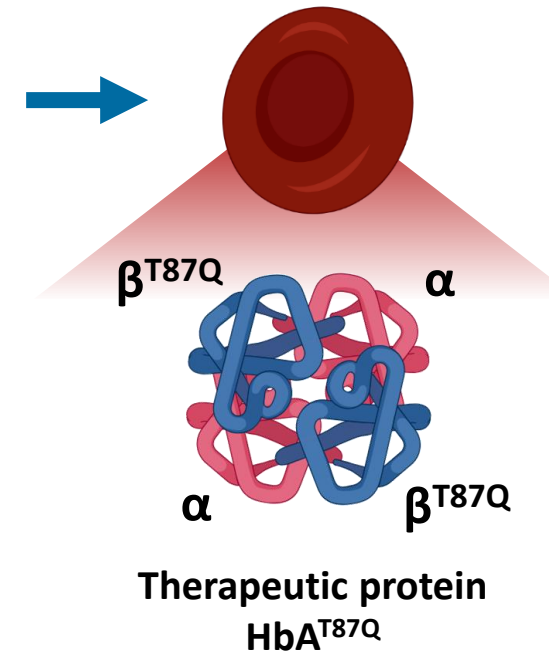
Patient HSCs transduced with the BB305 LVV



Transduced HSCs infused after myeloablation



HSCs reconstitute functional RBCs



Northstar-3 (HGB-212) Study

Phase 3 study of autologous CD34+ cells encoding β^{A-T87Q} -globin gene (LentiGlobin for β -thalassemia)

Key eligibility criteria

- Transfusion-dependent β -thalassemia
- β^0 or IVS-I-110 mutation at both alleles of the *HBB* gene
- ≤ 50 years of age

Primary endpoint: Transfusion Reduction

- $\geq 60\%$ reduction in RBC transfusion volume Month 12 – 24

Key secondary endpoint: Transfusion Independence

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

Follow-up: 2 years \rightarrow long-term follow-up study

Consented
N = 15

Screen failure
N = 1*

Stem Cell Mobilization Complete

N = 14

DP manufacturing and
infusion pending
N = 3

LentiGlobin Infused
N = 11

Target enrollment: 15 patients

Median follow-up: 5.4 months
(min – max: 1.5 – 15.9)

*Patient had LIC > 15 , but was then re-screened

HGB-212: Patient characteristics

Patient Characteristics

		N = 11
Genotypes n, (%)	β^0/β^0	7 (64)
	β^0 /IVS-I-110	2 (18)
	IVS-I-110/IVS-I-110	2 (18)
Gender		6 Male 5 Female
Age at consent median (min – max), yrs		17 (7 – 33)
Liver iron concentration median (min – max), mg Fe/g dw		4.9 (1.2 – 13.2)
Cardiac T2* median (min – max), msec		39.0 (16.6 – 74.7)
Splenectomy n, %		1 (9)

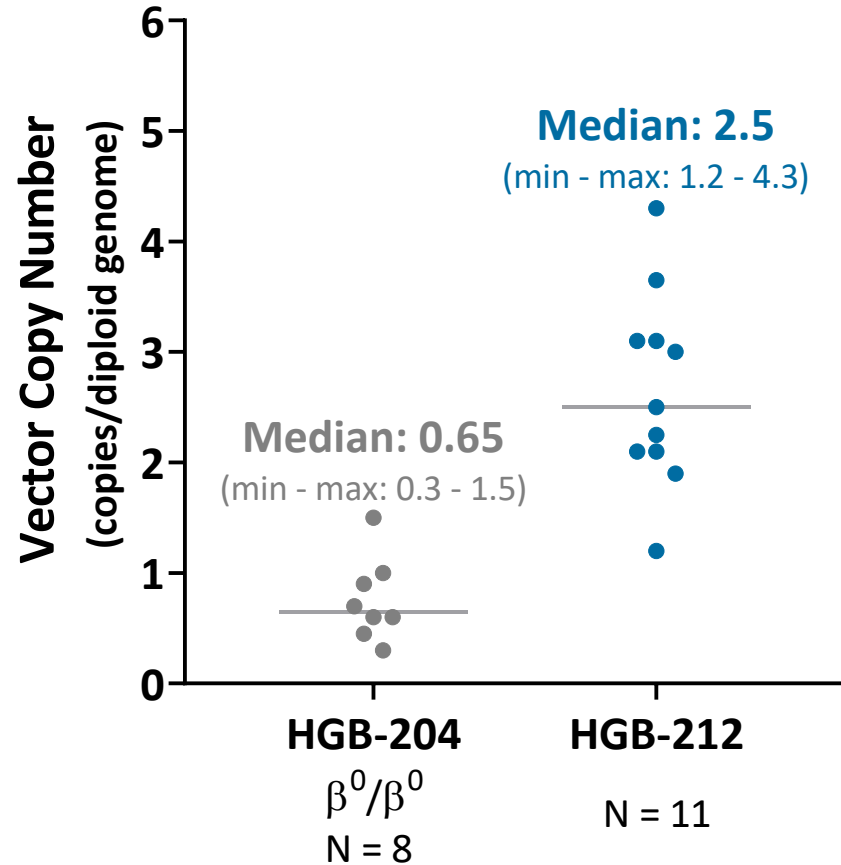
Transfusion History

		N = 11
Pre-study RBC transfusion volume median (min – max), mL/kg/yr		175.5 (74.6 – 211.0)
Pre-study number of RBC transfusions median (min – max), n/yr		17.5 (11.0 – 39.5)
Weighted average nadir Hb that preceded transfusions median (min – max), g/dL		9.7 (8.2 – 10.7)

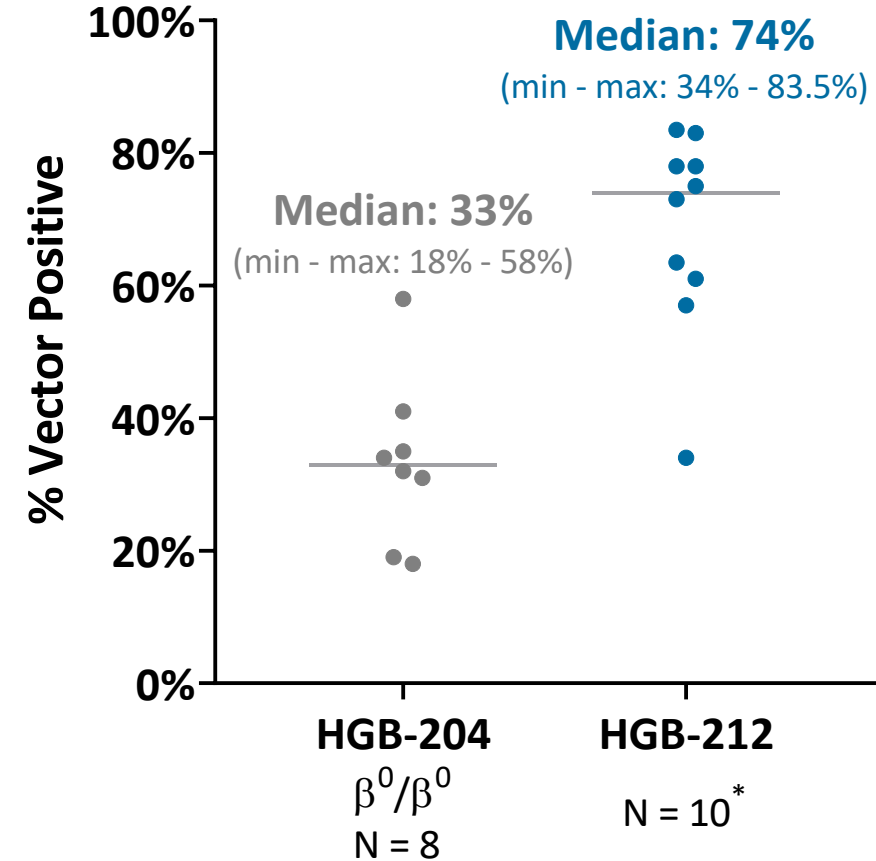
Retrospective data two years prior to study enrollment

Refined manufacturing has improved drug product characteristics

Vector copy number in drug product



% transduced cells in drug product



Median cell dose in HGB-212: 11.1×10^6 CD34+ cells/kg (min – max: $5.9 - 15.8 \times 10^6$ CD34+ cells/kg)

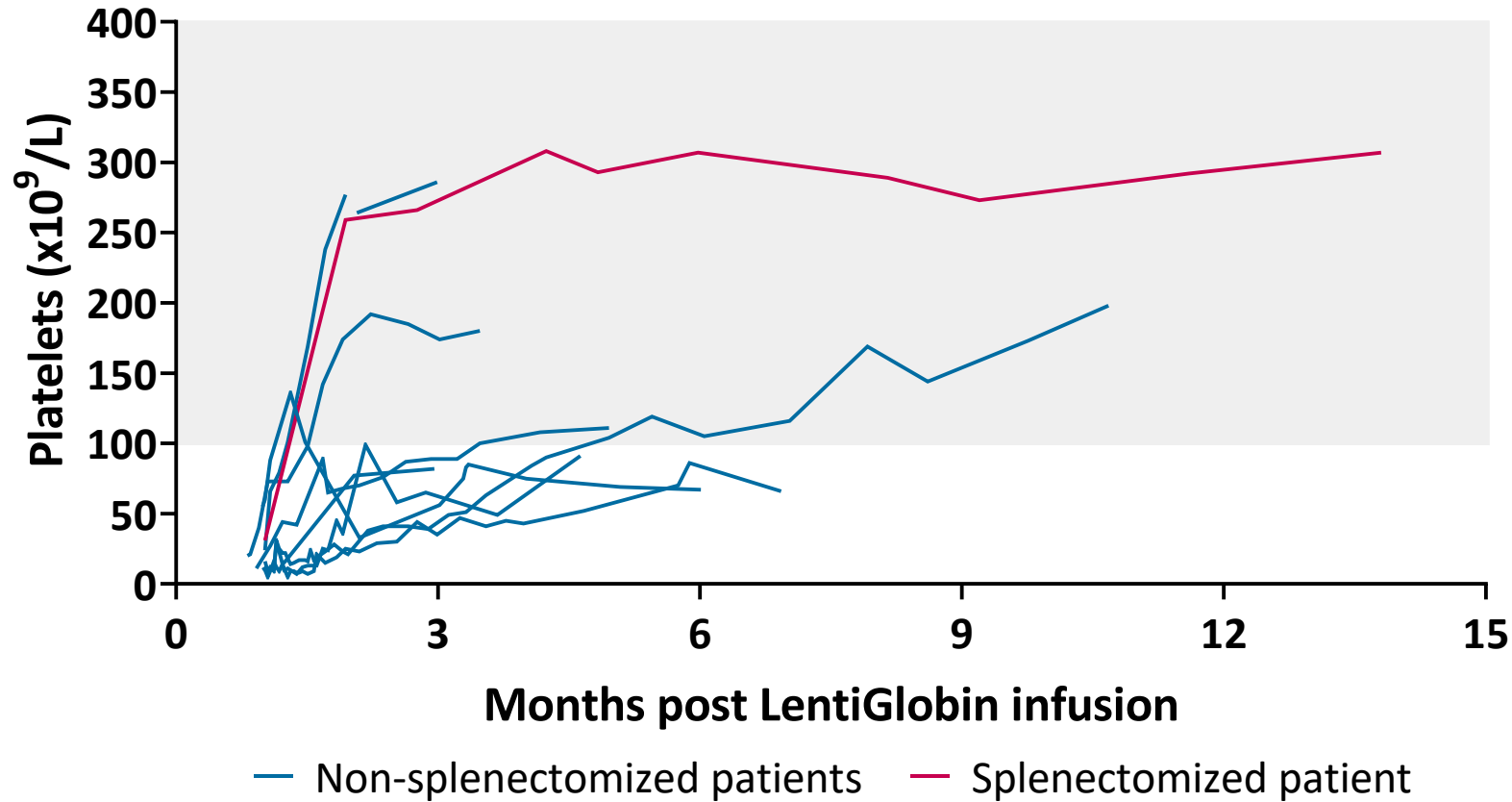
HGB-212: Treatment characteristics

	Median (min – max) N = 11
Busulfan conditioning	
AUC, $\mu\text{M} \cdot \text{min}$	4372 (3824 – 9087)
q6h dosing, n (%)	6 (55)
q24h dosing, n (%)	5 (45)
Neutrophil engraftment	26
ANC ≥ 500 cells/ μL x 3 days, days	(14 – 48)
Platelet engraftment[†]	36
Platelets $\geq 20\text{k}/\mu\text{L}$, days	(25 – 64)

Target busulfan AUC: q24h: 4200 (min – max: 3800 – 4500) $\mu\text{M} \cdot \text{min}$; q6h: 1050 (min – max: 950 – 1125) $\mu\text{M} \cdot \text{min}$.

[†]n=8; 3 patients with 1 – 3 months follow-up had not achieved platelet engraftment as of the datacut.

HGB-212: Platelet kinetics following myeloablative conditioning



Bleeding AEs

- One grade 3 bleeding AE of epistaxis from DP infusion to platelet engraftment
- No grade ≥ 3 bleeding AEs after platelet engraftment
- No serious bleeding events after LentiGlobin infusion

8/9 patients had platelets $> 50 \times 10^9/L$ by month 3

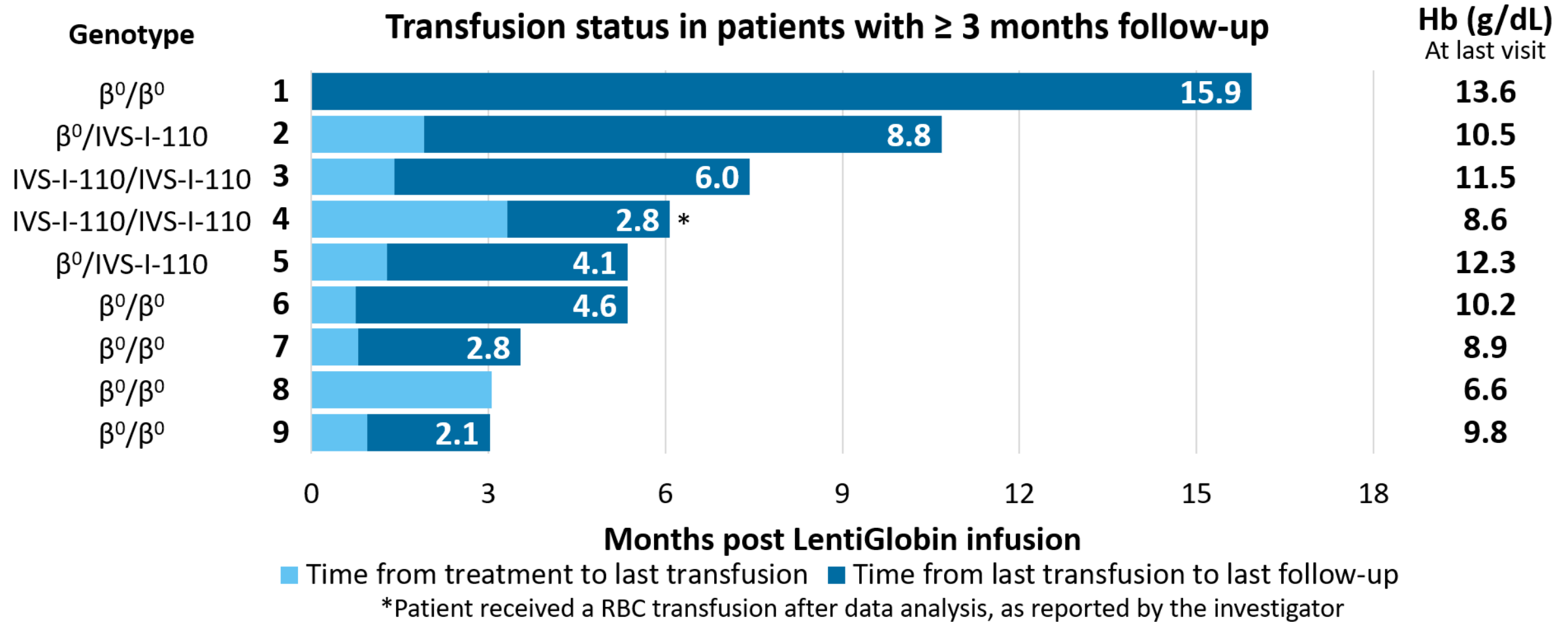
HGB-212: LentiGlobin safety profile is generally consistent with myeloablative conditioning

Non-hematologic grade \geq 3 AEs*		N = 11
<i>Post LentiGlobin infusion in \geq 2 patients</i>		n (%)
Febrile neutropenia		5 (46)
Stomatitis		5 (46)
Pharyngeal inflammation		2 (18)
Serious AEs		
<i>Post LentiGlobin infusion in \geq 1 patient</i>		
Pyrexia		2 (18)
Congestive heart failure		1 (9)
Febrile neutropenia		1 (9)
Headache		1 (9)
Neutropenia		1 (9)
Stomatitis		1 (9)
Thrombocytopenia		1 (9)

*Hematologic AEs commonly observed post-transplant have been excluded.
AEs, adverse events; Gr, grade

- AEs considered possibly related to LentiGlobin:
 - Abdominal pain (Gr 1)
 - Leukopenia (Gr 2)
 - Thrombocytopenia (Gr 2)
- No cases of veno-occlusive liver disease reported
- No graft failure or deaths

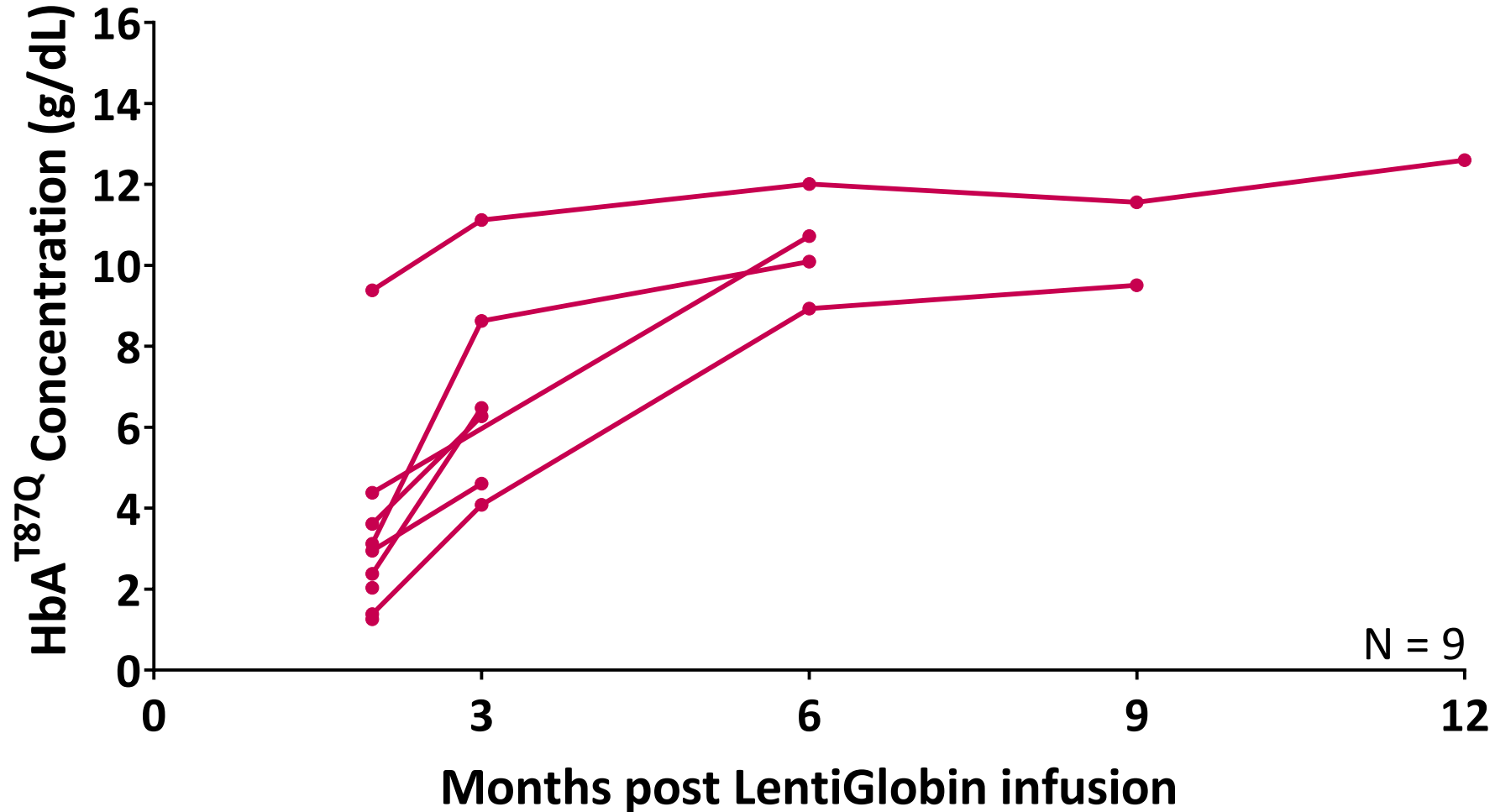
HGB-212: Hb of 10.2 – 13.6 g/dL in patients off RBC transfusions for ≥ 3 months (n=5)



Patient 1 achieved protocol definition of transfusion independence
 Weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months

HGB-212: HbA^{T87Q} in patients following treatment with LentiGlobin

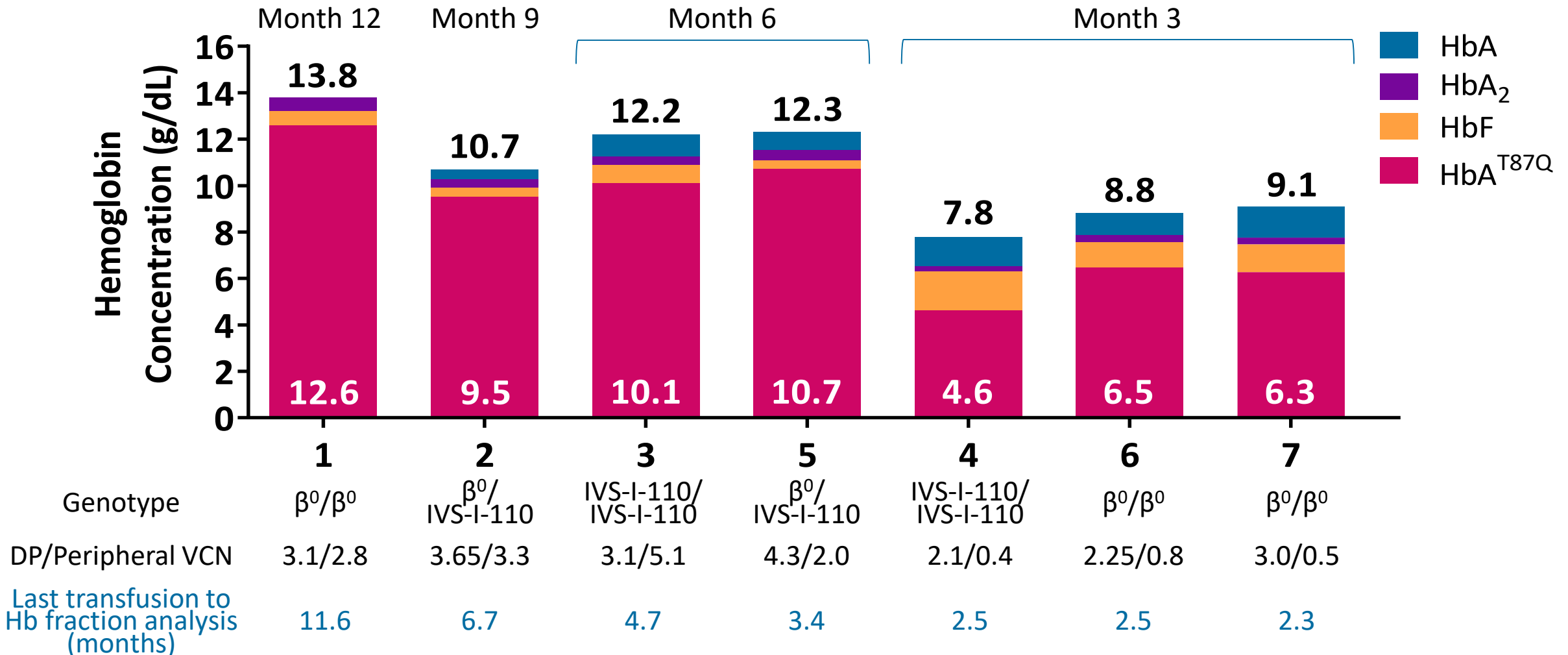
All patients at month 6 have HbA^{T87Q} \geq 8 g/dL (n=4)



HGB-212: Gene therapy-derived HbA^{T87Q} significantly contributes to Hb

59 – 91% of total Hb is HbA^{T87Q}

Hb fractions in patients with ≥ 3 month visit



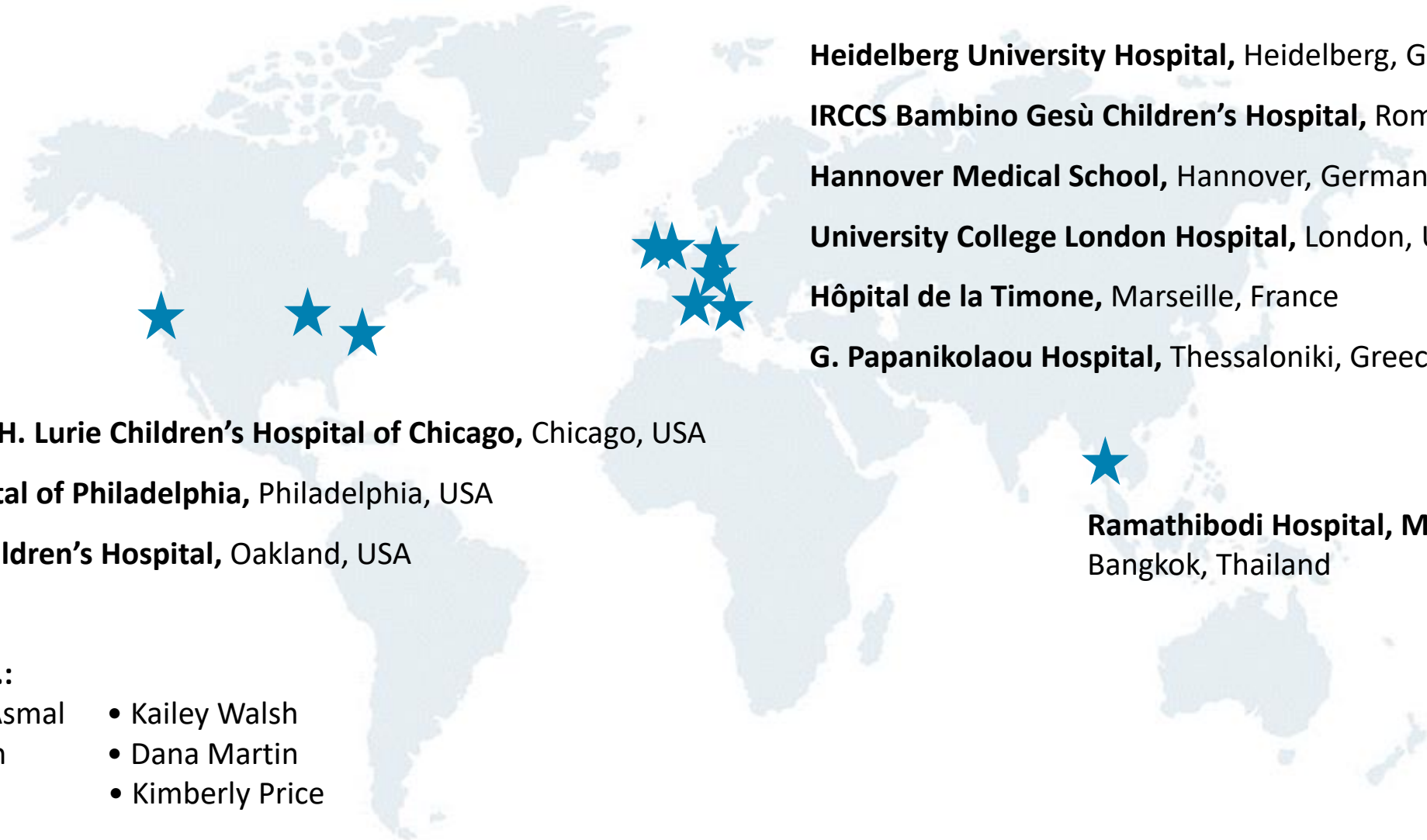
HGB-212: Summary

- The safety profile of LentiGlobin gene therapy was generally consistent with myeloablative busulfan-containing conditioning
- DP VCNs were substantially increased in HGB-212 vs HGB-204 resulting in higher HbA^{T87Q}
 - HbA^{T87Q} \geq 9.5 g/dL at last visit in patients with at least Month 6 Hb fraction (n=4)
 - HbA^{T87Q} levels increase until 6 months after DP infusion then stabilize
- Patients off RBC transfusions for \geq 3 months had total Hb 10.2 – 13.6 g/dL at last visit (n=5)
- The only patient with \geq 12 months follow-up to date achieved transfusion independence

Transfusion independence was defined as weighted average Hb \geq 9 g/dL without RBC transfusions for \geq 12 months.

DP, drug product; Hb, hemoglobin; RBC, packed red blood cells; TDT, transfusion-dependent β -thalassemia; VCN, vector copy number

Thank you to the study participants and their families



Heidelberg University Hospital, Heidelberg, Germany

IRCCS Bambino Gesù Children's Hospital, Rome, Italy

Hannover Medical School, Hannover, Germany

University College London Hospital, London, UK

Hôpital de la Timone, Marseille, France

G. Papanikolaou Hospital, Thessaloniki, Greece



**Ramathibodi Hospital, Mahidol University,
Bangkok, Thailand**

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

bluebird bio, Inc.:

- Mohammed Asmal
- Marisa Gayron
- Ruiting Guo
- Kailey Walsh
- Dana Martin
- Kimberly Price