EHA 2019 Abstract S1632

Safety and Efficacy of LentiGlobin gene therapy in patients with transfusion-dependent β-thalassemia and non-β^0/β^0 genotypes in the phase 3 Northstar-2 study

Franco Locatelli, Alexis A. Thompson, Suradej Hongeng, John B. Porter, Martin G. Sauer, Janet L. Kwiatkowski, Adrian J. Thrasher, Isabelle Thuret, Heidi Elliot, Ge Tao, Richard A. Colvin, Mark C. Walters

DISCLOSURE OF AFFILIATIONS

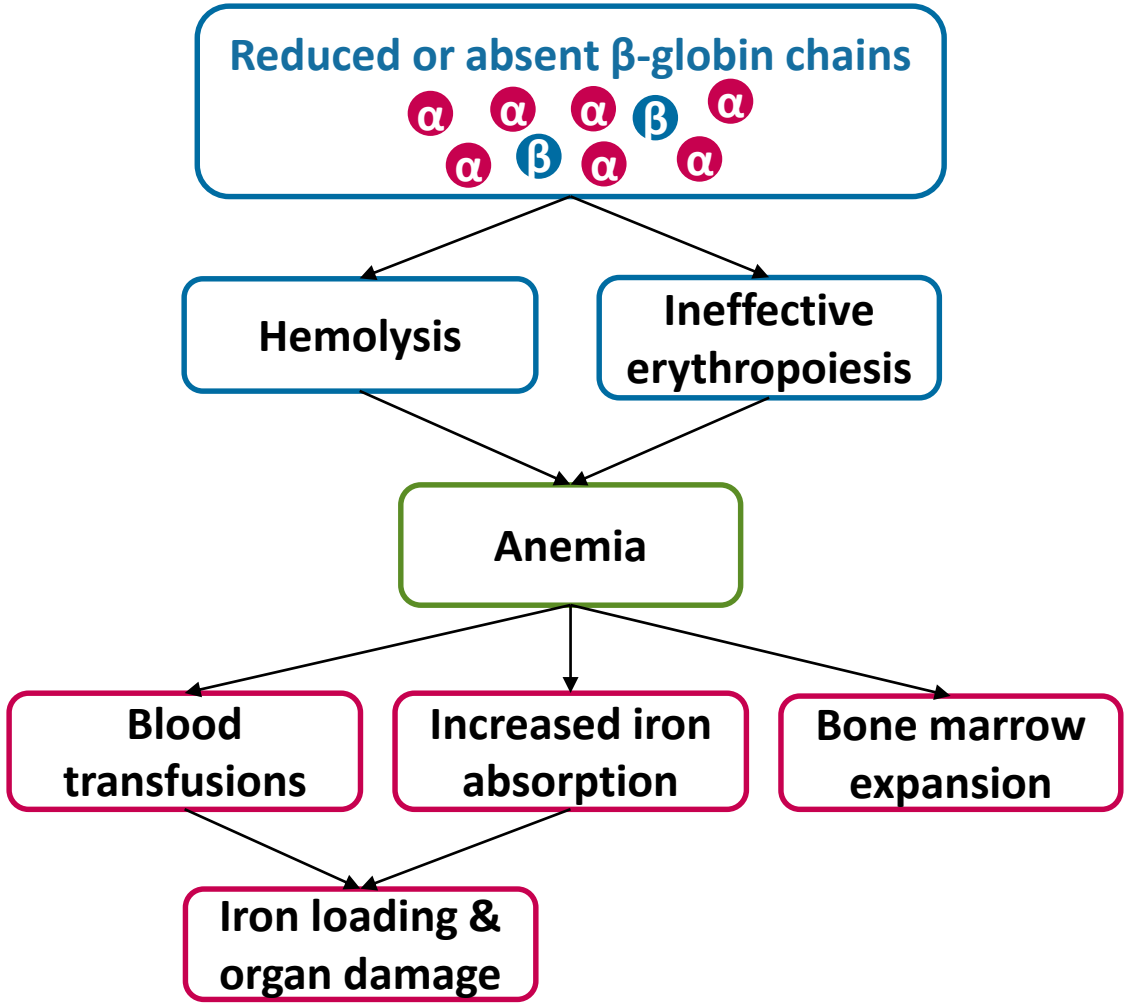
F. Locatelli

Disclosures

Amgen: Honoraria, advisor
Bellicum: Consultancy, advisor
bluebird bio: Consultancy
Miltenyi: Honoraria
Novartis: Consultancy, advisor

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

- Endemic in South Asia, the Middle East, North Africa, and Southern Europe[1-3]
  - Migration is changing the global distribution of the disease
- Patients with transfusion-dependent β-thalassemia (TDT) require lifelong blood transfusions for survival[1-3]
  - Iron overload
  - Organ damage
- Allo-HSCT is potentially curative but is limited by donor availability and is associated with transplant-related risk (especially in patients older than 14 years)[1]



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

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

Key eligibility criteria

- Transfusion-dependent β-thalassemia
- Non-β^0/β^0 genotype
- ≤ 50 years of age

Primary endpoint: **Transfusion Independence**

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

Target enrollment: **23 patients**

Consented
N=31

Ineligible
N=8*

Mobilization pending
N=1

Stem Cell Mobilization Complete
N=22

Discontinued
N=1†

Drug product manufacture and infusion pending
N=1

LentiGlobin Infused
N=20
Median follow-up: 8.1 months
(min – max: 0.5 – 22.2)

*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

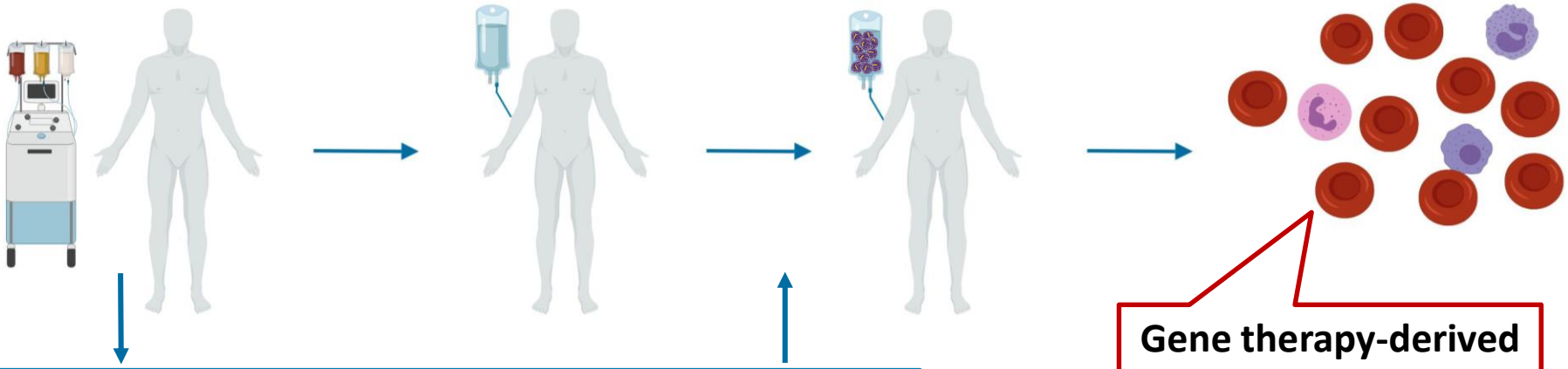
HGB-207: Study design

HSC collection
Mobilization (G-CSF + plerixafor) & apheresis

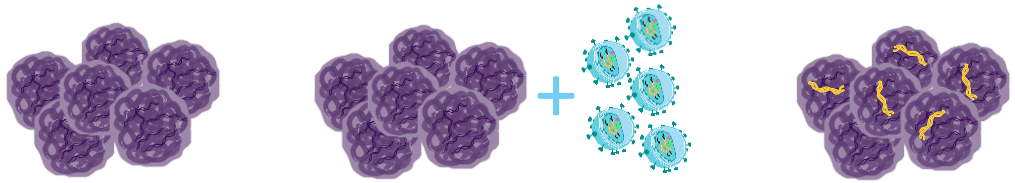
Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and reconstitute functional RBCs



LentiGlobin centralized manufacturing

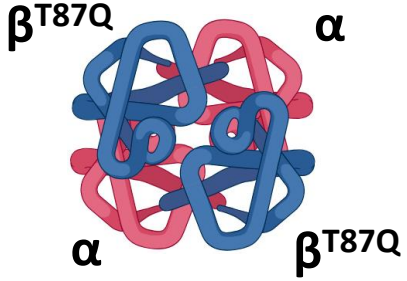


Select CD34+ cells

Transduce with BB305 lentiviral vector

Cryopreserve, test, release DP

Gene therapy-derived HbA^{T87Q}



2-yr Follow-up

Long-Term Follow-Up Study

DP, drug product; G-CSF, granulocyte-colony stimulating factor; HSC, hematopoietic stem cell; RBC, red blood cell

HGB-207: Patient characteristics

20 patients treated

Patient Characteristics		
Genotypes n, (%)	β^{+}/β^{0} β^{E}/β^{0} β^{+}/β^{+}	**10** (50) **6** (30) **4** (20)
Gender		**11 Males** **9 Females**
Age at consent median (min – max), yrs		**16** (8 – 34)
Liver iron content median (min – max), mg Fe/g dw		**5.5** (1.0 – 41.0)
Cardiac T2* median (min – max), msec		**36.5** (20.6 – 50.9)
Splenectomy n, %		**4** (20)

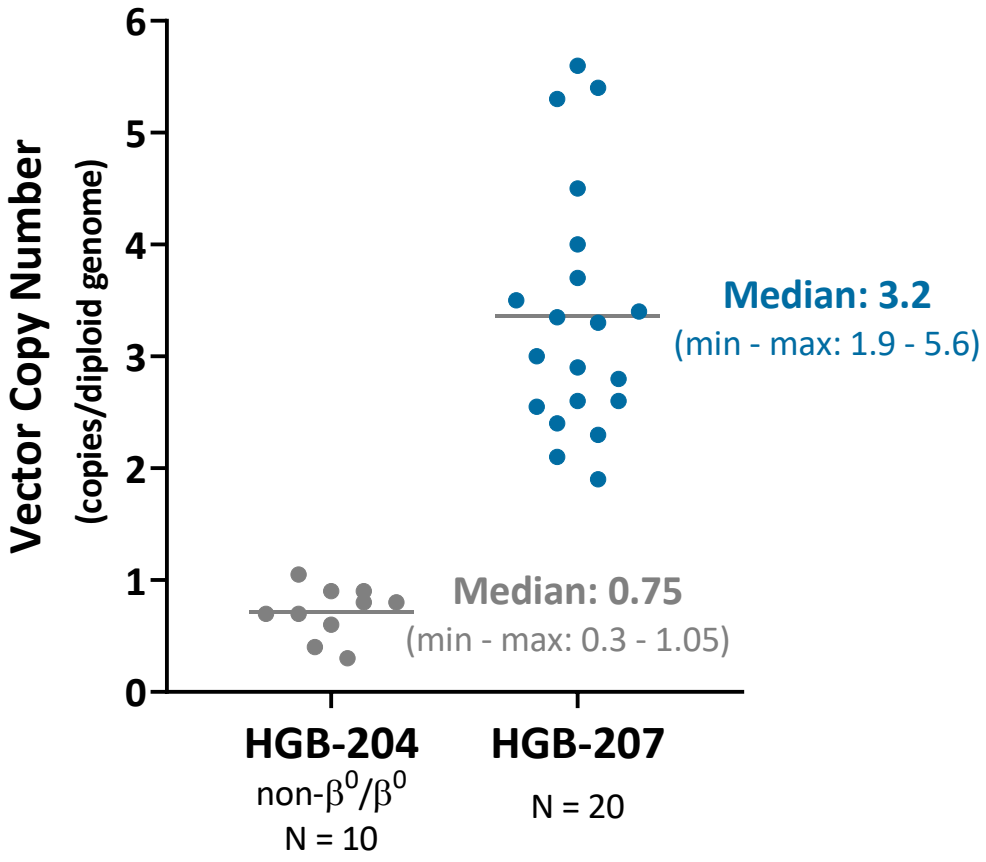
Transfusion History	median (min – max)
Pre-study RBC transfusion volume mL/kg/yr	**200.8** (152.3 – 274.4)
Pre-study number of RBC transfusions n/yr	**17.3** (11.5 – 37.0)
Weighted average nadir Hb preceding transfusions g/dL	**9.6** (7.5 – 11.0)

Retrospective data 2-years prior to study enrollment

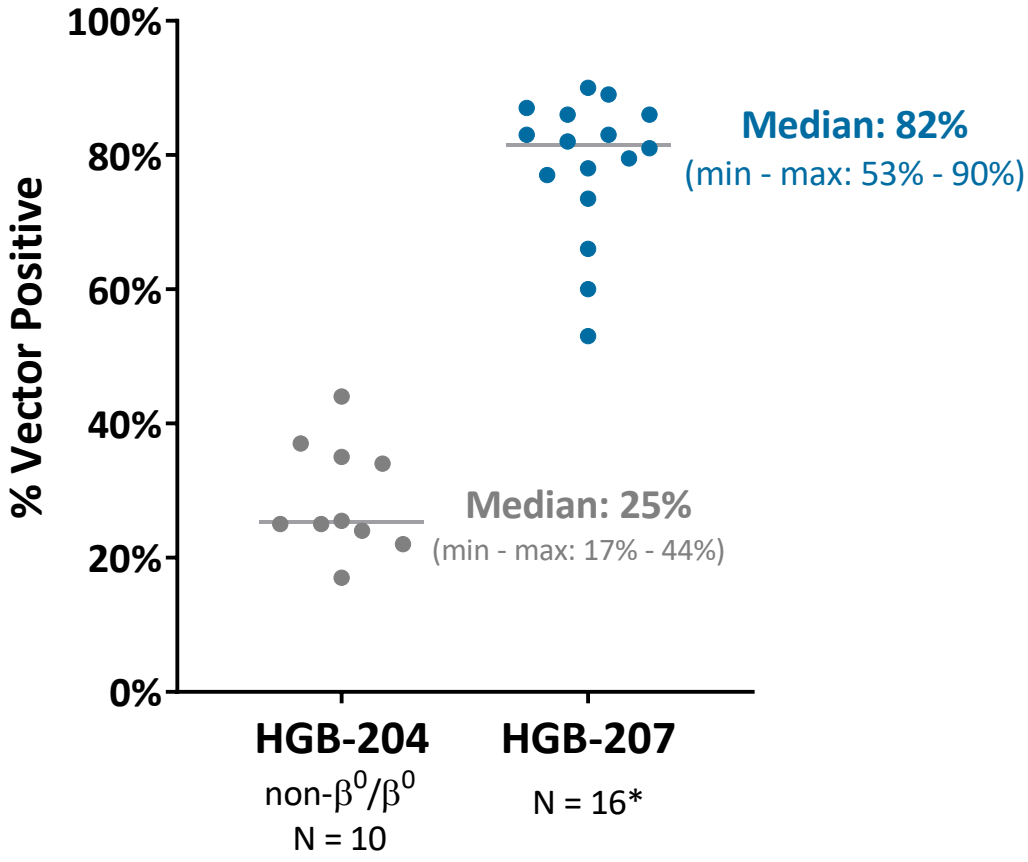
Hb, hemoglobin; RBC, red blood cells

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

VCN in drug product



Proportion of CD34+ cells transduced



Median cell dose in HGB-207: 8.0 x10^6/kg CD34+ cells (min – max: 5.0 – 19.9 x10^6/kg CD34+ cells)

*Four % vector positive values were not available at time of datacut

HGB-207: Treatment characteristics

20 patients treated

Treatment Characteristics	
	median (min – max)
Busulfan AUC[†] Daily average over 4 days, µM*min	**4471** (3709 – 8947)
Neutrophil engraftment[‡] ANC ≥ 500 cells/µL x 3 days, days	**22.5** (13 – 32)
Platelet engraftment[^] Platelets ≥ 20k/µL, days	**45** (20 – 84)

[†]N=19, Busulfan AUC was not available for 1 patient as of datacut

[‡]N=18, 2 patients with < 1 month of follow-up had not engrafted as of datacut

[^]N=15, 5 patients with < 1 – 4.9 months of follow-up had not engrafted as of datacut

ANC, absolute neutrophil count; AUC, area under the curve

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

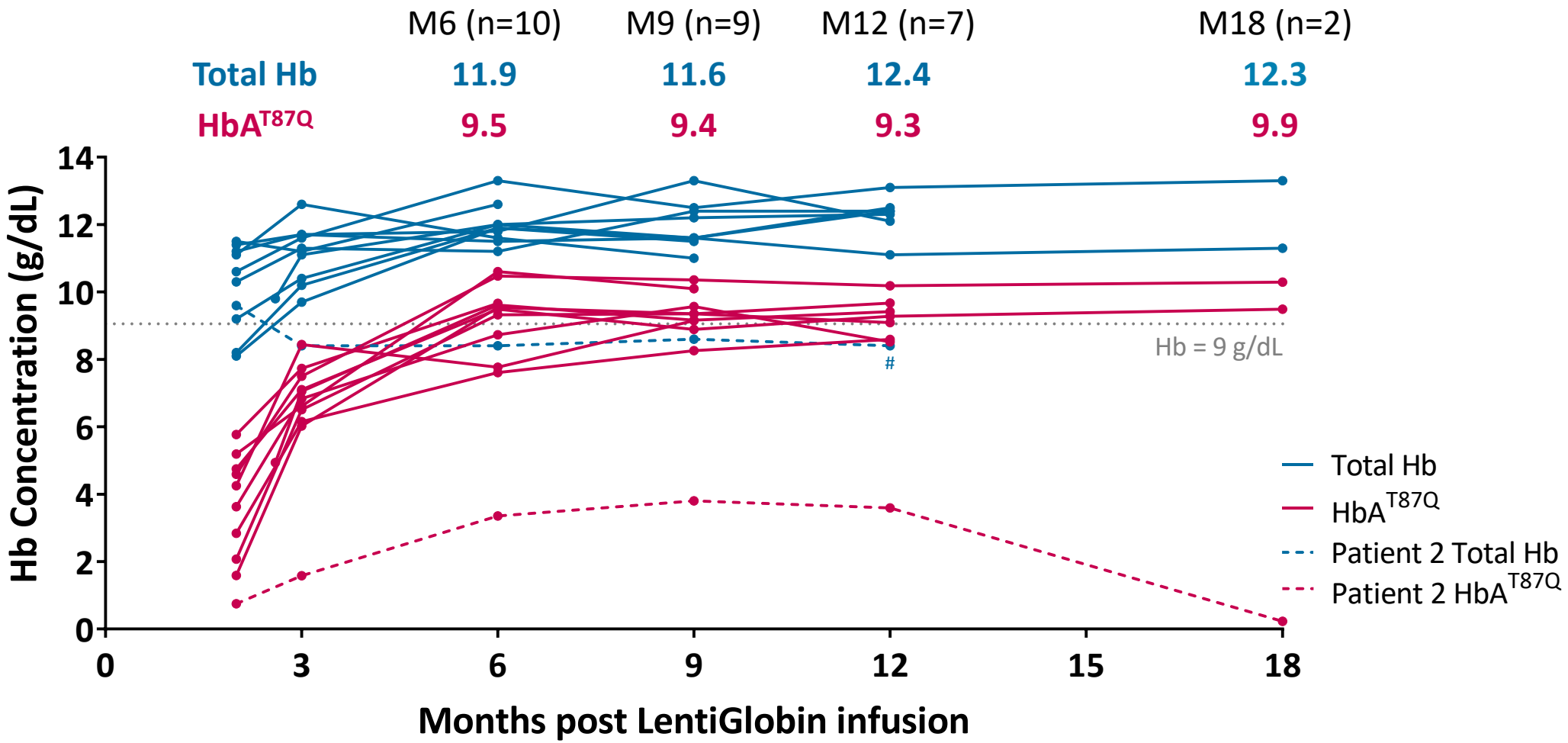
Non-hematologic grade ≥ 3 AEs* *Post LentiGlobin infusion in ≥ 3 patients*	**N = 20 n (%)**
Stomatitis	12 (60)
Febrile neutropenia	6 (30)
Pyrexia	4 (20)
Epistaxis	3 (15)
Veno-occlusive liver disease	3 (15)
Serious AEs *Post LentiGlobin infusion in ≥ 1 patient*	
Veno-occlusive liver disease	3 (15)
Pyrexia	2 (10)
Thrombocytopenia	2 (10)
Febrile neutropenia	1 (5)
Hypotension	1 (5)
Hypoxia	1 (5)
Lower respiratory tract infection	1 (5)
Neutropenia	1 (5)
Neutropenic sepsis	1 (5)
Sepsis	1 (5)
Stomatitis	1 (5)
Transfusion reaction	1 (5)

- Three serious grade 4 VODs attributed to conditioning
  - All were treated with defibrotide and resolved
- One serious grade 3 thrombocytopenia AE was considered possibly related to LentiGlobin
  - Platelet count at last visit was 63 $x10^9$/L (Month 7)
- No graft failure or deaths
- No vector-mediated replication competent lentivirus detected
- No early evidence of clonal dominance

*Hematologic AEs commonly observed post-transplant have been excluded; AE, adverse event; VOD, veno-occlusive liver disease

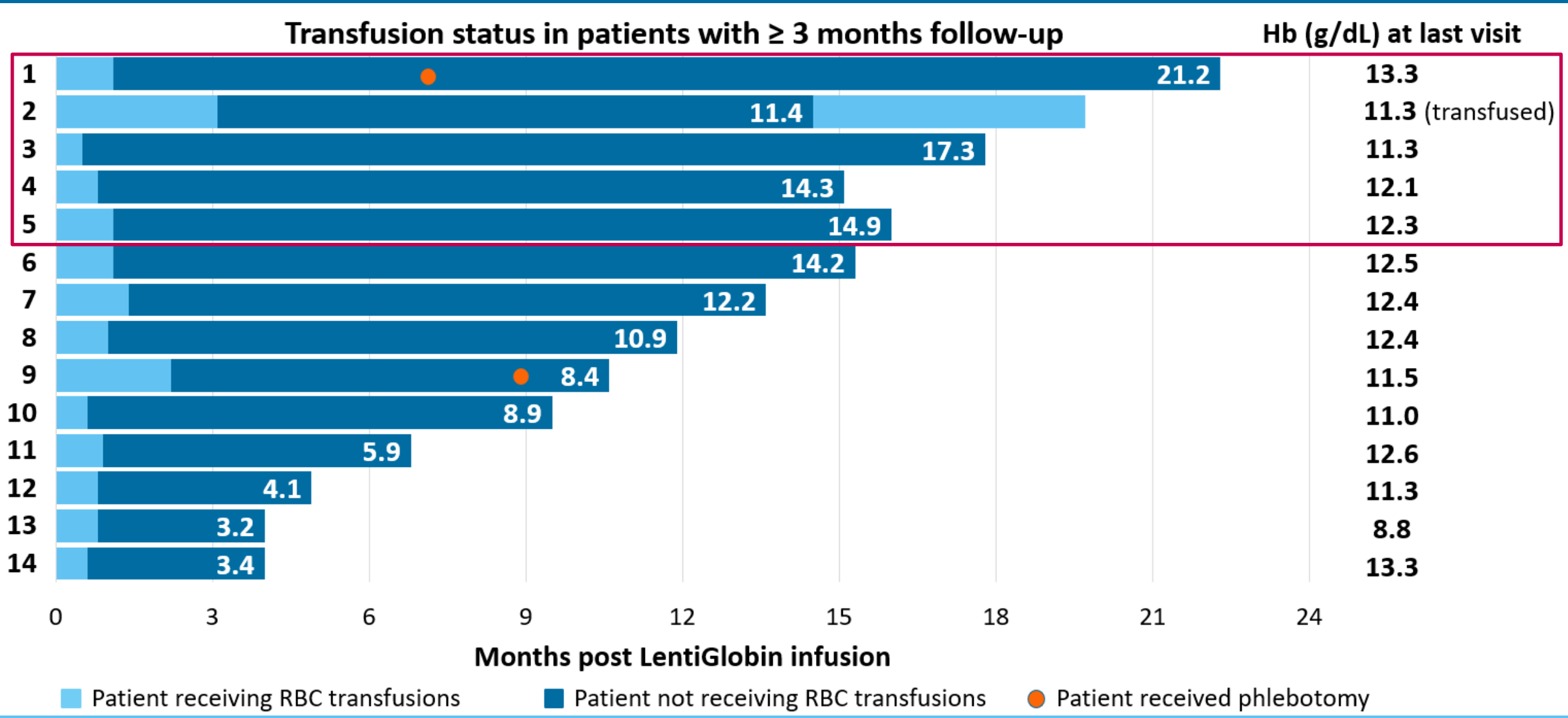
HGB-207: Stable total Hb and gene therapy-derived HbA^{T87Q} in 10/11 patients with ≥ 6 months follow-up

Median Hb in patients free from transfusions at last study visit (g/dL)



#Last Hb before patient 2 restarted red blood cell transfusions; Hb, hemoglobin

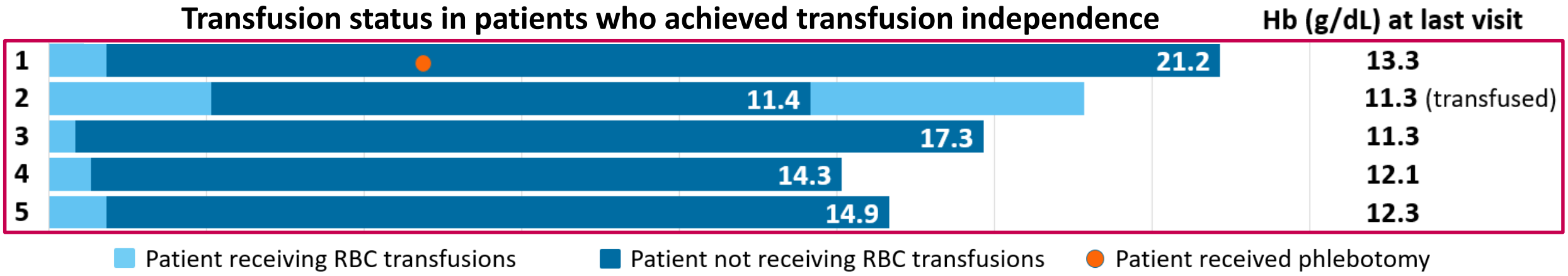
HGB-207: 13/14 patients with ≥ 3 months follow-up are transfusion free



Hb, hemoglobin; RBC, red blood cell

Data as of 13 December 2018

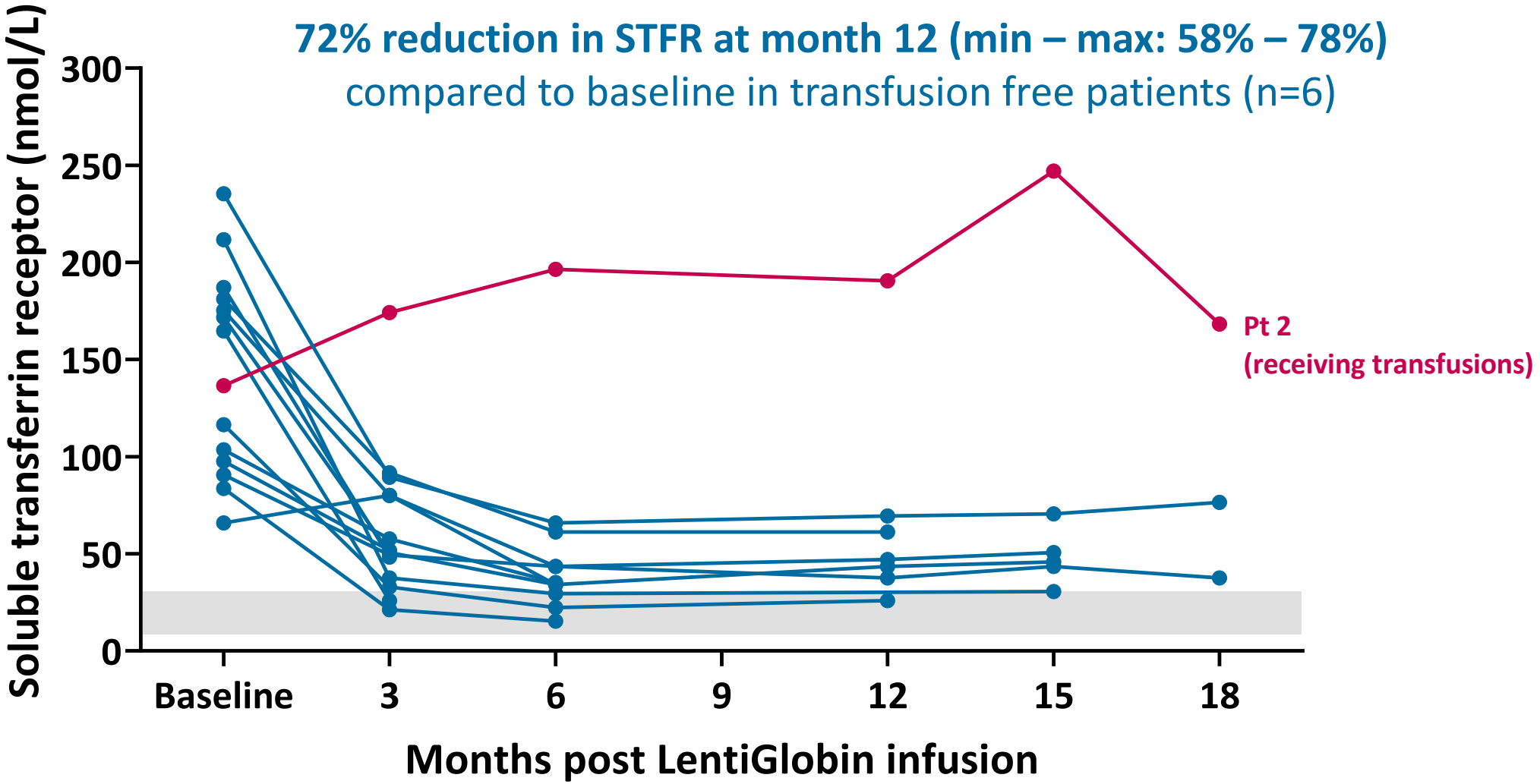
HGB-207: 4/5 (80%) evaluable patients achieved the primary endpoint of transfusion independence



- **4/5 (80%) evaluable patients achieved the primary endpoint of transfusion independence**
  Weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months
- **Median duration of TI: 13.6 months** (min – max: 12.0 – 18.2 months)
  All responses are ongoing
- **Median weighted average Hb during TI of 12.4 g/dL** (min – max: 11.5 – 12.6 g/dL)

Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence

HGB-207: Improvement in erythropoiesis post LentiGlobin
STFR normalizes in patients who stopped transfusions

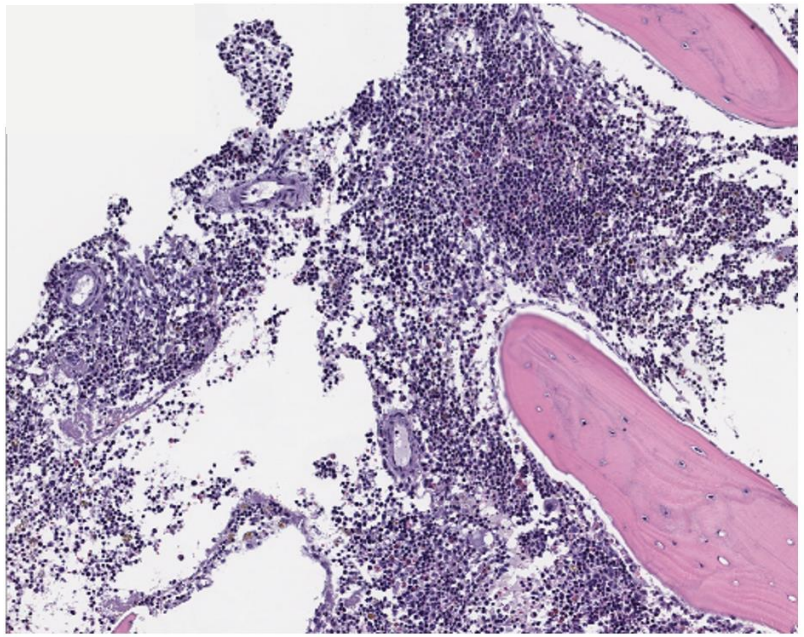


STFR, soluble transferrin receptor

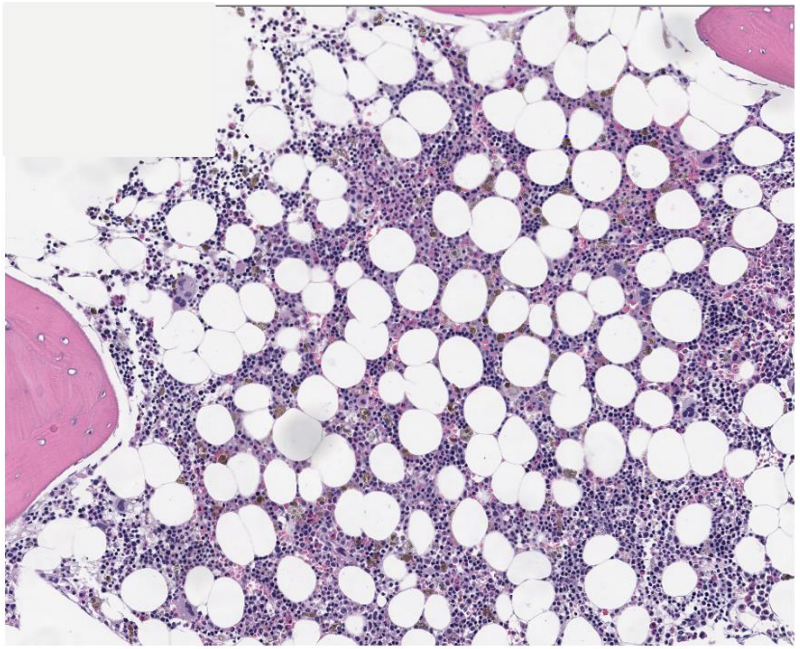
HGB-207: Improvement in erythropoiesis post LentiGlobin
Improvement in bone marrow histology and M:E ratio

Patient 1 (20 yr-old) bone marrow analysis

Screening

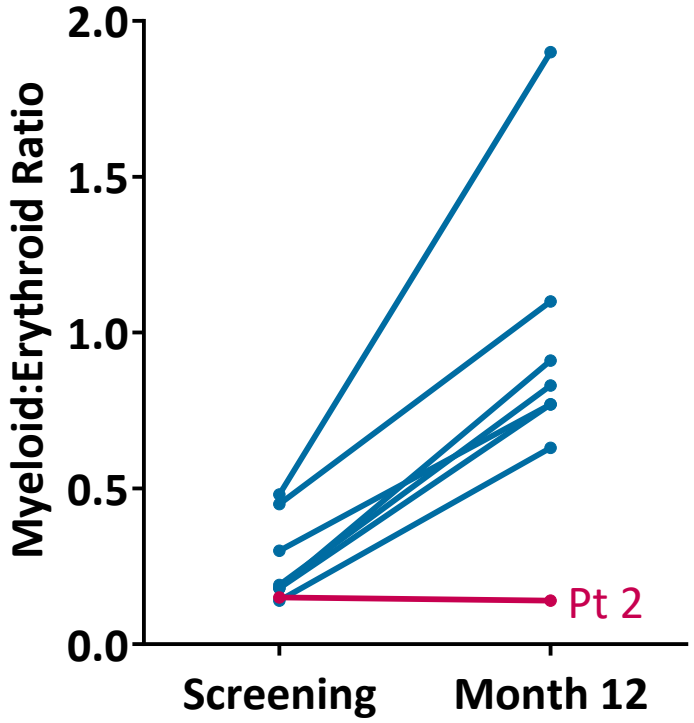


Month 12 post-LentiGlobin



Hb at Month 12: 13.1 g/dL

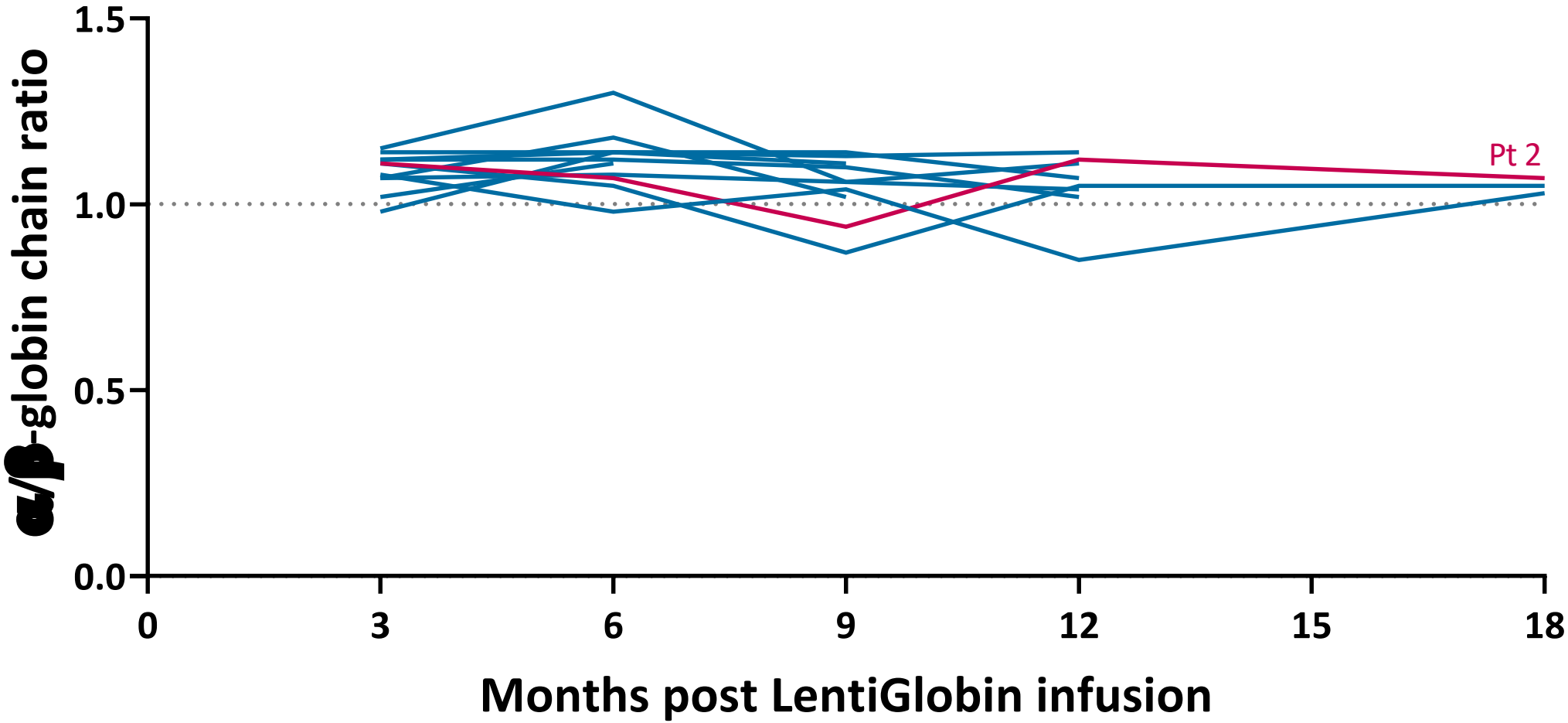
Myeloid:Erythroid ratio following LentiGlobin gene therapy (n=8)



Normal M:E Ratio[1]: 3-4:1

1. Origa R. GeneReviews®. 2018.

HGB-207: α/β-globin chain ratio is normal after stopping RBC transfusions



- In patients with β-thalassemia, the α/β-globin chain ratio is higher due to absent or reduced β-globin synthesis

HGB-207: Summary

- 13/14 patients with ≥ 3 months follow-up after LentiGlobin gene therapy are transfusion free
- 4/5 evaluable patients achieved primary endpoint of transfusion independence
  - Weighted average Hb during TI of 12.4 g/dL
- HbA^{T87Q} stabilizes approximately 6 months after LentiGlobin infusion
  - Median HbA^{T87Q} at Month 6 and 12 of 9.5 g/dL (n=10) and 9.3 g/dL (n=7)
- Patients who stopped RBC transfusions show improvement in erythropoiesis and normal α/β-globin chain ratio
- The safety profile of LentiGlobin gene therapy remains generally consistent with myeloablative busulfan conditioning
  - Three serious AEs of veno-occlusive liver disease
  - One grade 3 thrombocytopenia was considered possibly related to LentiGlobin
- LentiGlobin received EU approval for patients ≥ 12 years of age with TDT who do not have a β^0/β^0 genotype for whom HSCT is appropriate, but an HLA-matched donor is not available

AE, adverse event; EU, European Union; Hb, hemoglobin; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence (weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months)

Thank you to the study participants and their families

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

IRCCS Bambino Gesù Children's Hospital, Rome, Italy

Hannover Medical School, Hannover, Germany

University College London Hospital, London, UK

UCL Great Ormond Street Hospital, London, UK

Hôpital de la Timone, Marseille, France

Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

bluebird bio, Inc.:

- Kailey Walsh
- Marisa Gayron
- Kimberly Price
- Dana Martin
- Sue Chen
- Joan Zape