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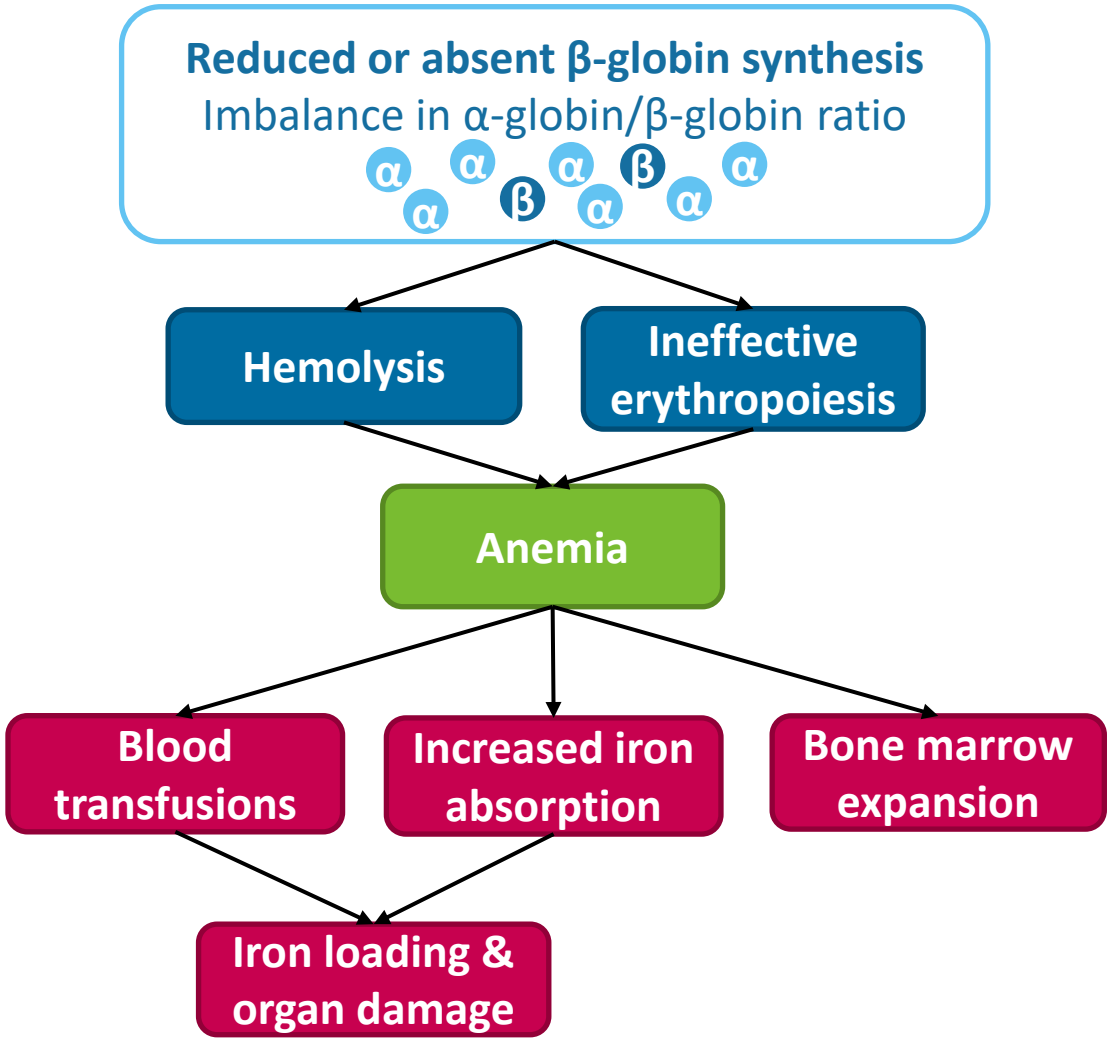
LentiGlobin Gene Therapy in Transfusion-Dependent β-Thalassemia Patients with Non-β^0/β^0 Genotypes

Timothy S. Olson, Mark C. Walters, Janet L. Kwiatkowski, Suradej Hongeng, John E. J. Rasko, John B. Porter, Martin Sauer, Adrian J. Thrasher, Isabelle Thuret, Gary J. Schiller, Heidi Elliot, Briana Deary, Ying Chen, Ge Tao, Mohammed Asmal, Franco Locatelli, Alexis A. Thompson

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 to enable survival[1-3]
  - Iron overload
  - Organ damage
- Allo-HSCT is potentially curative, but is associated with transplant-related risk and donor limitations[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 (HGB-204) and Northstar-2 (HGB-207) Studies

HGB-204

non-β^0/β^0 genotypes and β^0/β^0 genotypes

Completed

Phase 1/2, international, open-label, single-arm study

Primary Efficacy Endpoints

- **≥ 2 g/dL of HbA^{T87Q} between Months 18 – 24**
- **Transfusion Independence**

All 18 patients infused

10 patients with non-β^0/β^0 genotypes

8 patients with β^0/β^0 genotypes

Median follow-up in patients with non-β^0/β^0 genotypes: 36.0 months

(min – max: 29.3 – 48.1 months)

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

HGB-207

non-β^0/β^0 genotypes

Ongoing

Phase 3, international, open-label, single-arm study

Primary Endpoint

Transfusion Independence

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

16 patients infused

Target: 23 patients

Median follow-up: 9.3 months

(min – max: 0.7 – 20.4 months)

Hb, hemoglobin

Data as of September 14, 2018

HGB-204 and HGB-207: Study design

Enrollment

204: non-β^0/β^0 or β^0/β^0 genotypes
12 – ≤ 35 yrs old

207: non-β^0/β^0 genotypes
≤ 50 yrs old

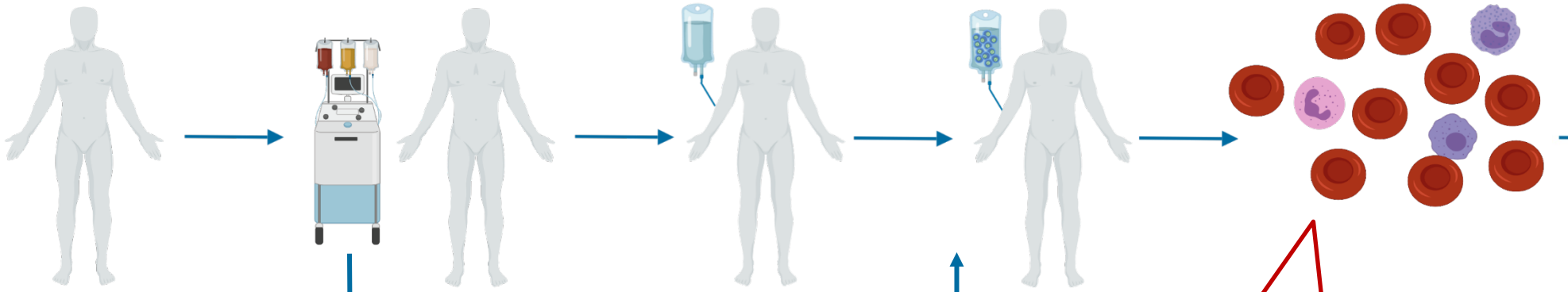
HSC collection

Mobilization
(G-CSF + plerixafor) &
apheresis

Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs

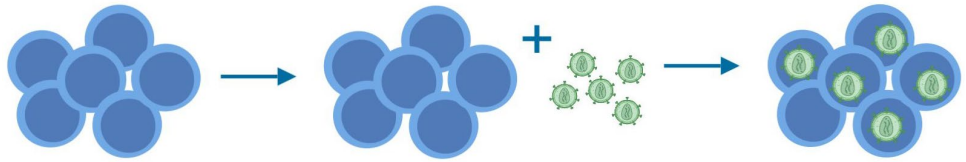


2-yr follow-up

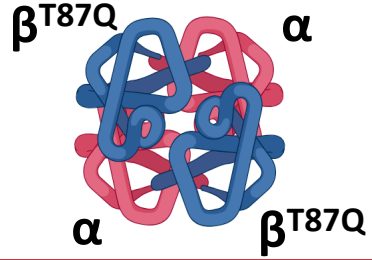
Long-Term Follow-Up Study

LentiGlobin DP centralized manufacturing

Refined manufacturing process used in HGB-207



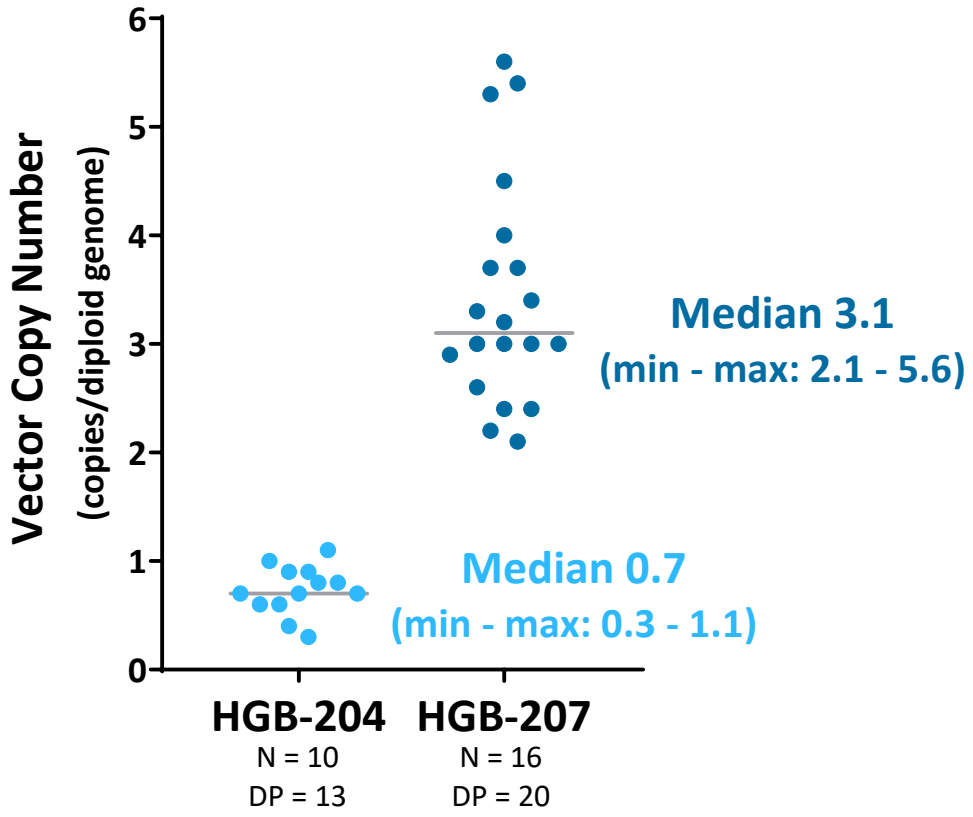
Gene therapy-derived HbA^{T87Q}



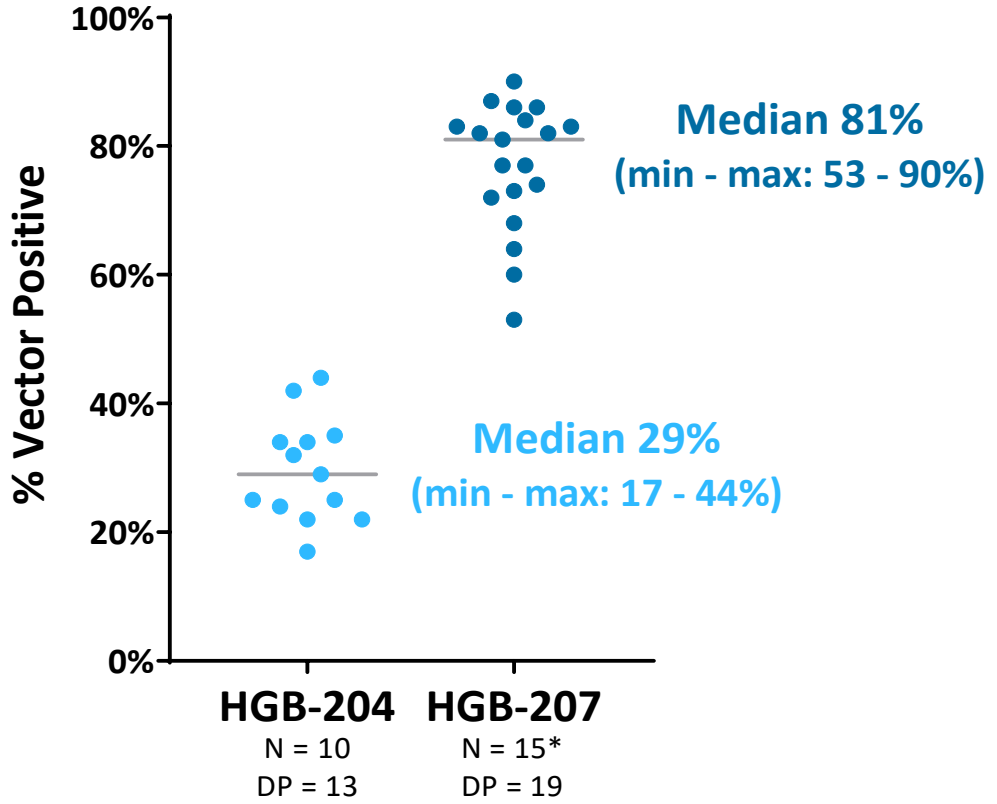
DP, drug product; G-CSF, granulocyte colony-stimulating factor; HSC, hematopoietic stem cell; RBC, red blood cell

Refined manufacturing yielded more favorable drug product characteristics

Vector copy number in drug product



Proportion of CD34+ cells transduced



Median cell dose:

HGB-204: 7.1 (min – max: 5.2 – 13.0) x 10^6 CD34+ cells/kg

HGB-207: 7.7 (min – max: 5.0 – 19.4) x 10^6 CD34+ cells/kg

*One DP did not have the %CD34+ cells transduced at datacut. Number of DP exceeds number of patients as some patients were mobilized twice.

HGB-204 and HGB-207: Patient and treatment characteristics

Patient Characteristics

		HGB-204 (N = 10)	HGB-207 (N = 16)
Genotypes	β^E/β^0	**6** (60)	**6** (38)
	β^+/β^0	**1** (10)	**7** (44)
	β^+/β^+	**2** (20)	**3** (19)
	Other	**1** (10)	–
Age at consent median (min – max), yrs		**19.5** (16 – 34)	**19** (8 – 34)
Patients < 18 yrs old, n (%)		**2** (20)	**7** (44)
Pre-study pRBC transfusion volume annualized median (min – max), mL/kg/yr		**151** (140 – 234)	**192** (152 – 274)
Liver iron concentration median (min – max), mg/g		**5.7** (1.2 – 26.4)	**6.4** (1.0 – 41.0)
Splenectomy, n, %		**3** (30)	**4** (25)

Treatment Characteristics

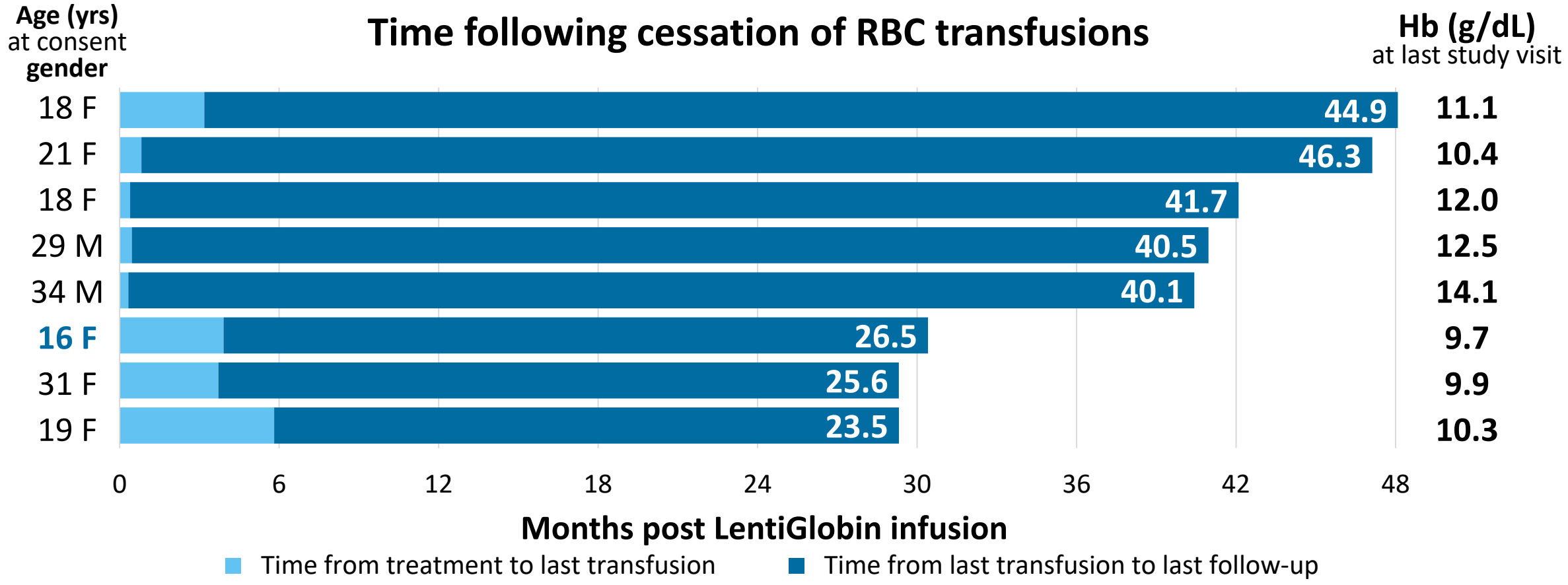
	HGB-204 (N = 10) median (min – max)	HGB-207 (N = 16) median (min – max)
Busulfan AUC estimated average x 4 days, µM*min	**4060** (3030 – 4417)	**4545** (3709 – 8947)
Neutrophil engraftment ANC ≥ 500 cells/µL x 3 days, days	**18.5** (14 – 27)	**19**[§] (13 – 32)
Platelet engraftment platelets >20k/µL, days	**50.5** (19 – 191)	**44.5**[§] (20 – 84)

Target busulfan AUC in 204 was 4000 (3600 – 5000) and in 207 was 4200 (3800 – 4500) µM*min after protocol amendment to lower AUC

[§]As of the datacut, 1 patient (1-month follow-up) and 4 patients (≤ 2 months follow-up) in HBG-207 had not achieved neutrophil and platelet engraftment, respectively.

AUC, area under the curve; pRBC, packed red blood cells

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

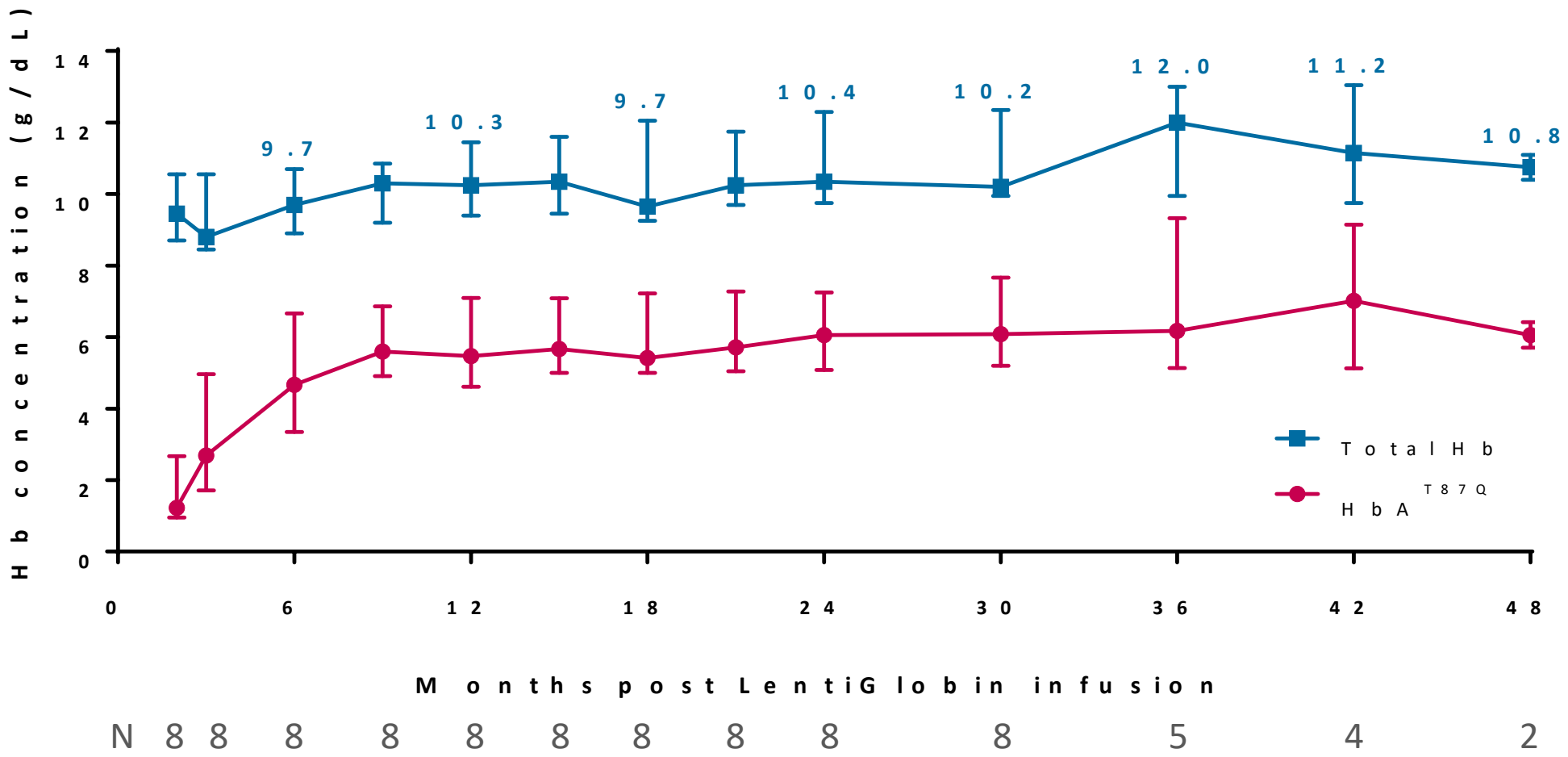


Median duration of TI: 38.0 months (min – max: 21.2 – 43.6 months)
Median weighted average Hb during TI: 10.2 g/dL (min – max: 9.3 – 13.2 g/dL)

Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence (weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months)

HGB-204: HbA^{T87Q} expression in blood is stable post-LentiGlobin in patients who achieved transfusion independence

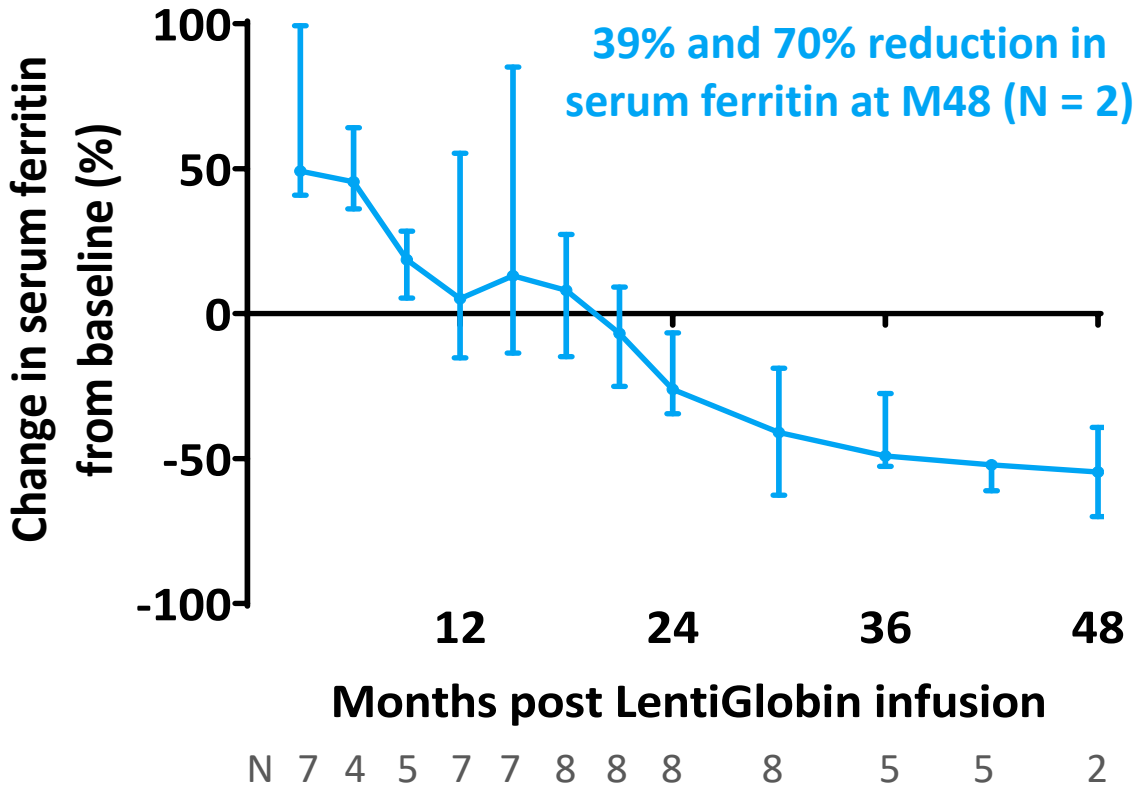
Median Hb in patients with non-β^0/β^0 genotypes who achieved transfusion independence

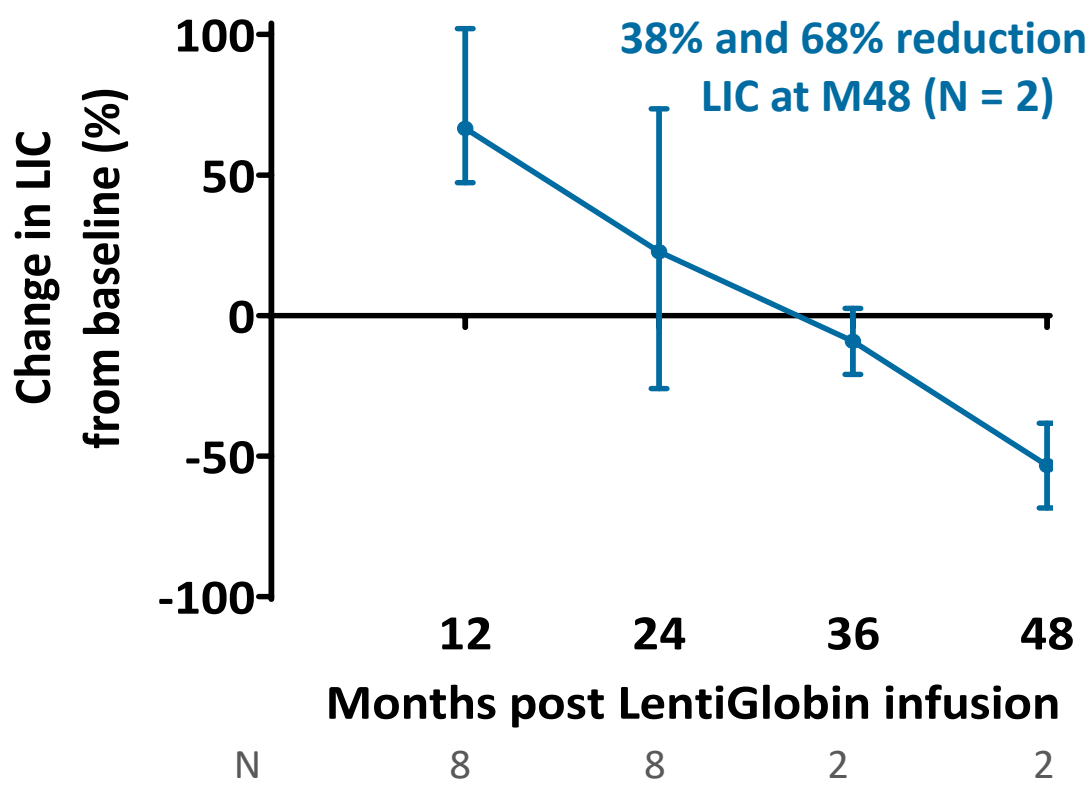


Medians (Q1, Q3) depicted; Hb, hemoglobin

HGB-204: Reduction in iron overload following LentiGlobin gene therapy

% Change in serum ferritin and LIC from baseline in patients with non-β^0/β^0 genotypes who achieved TI

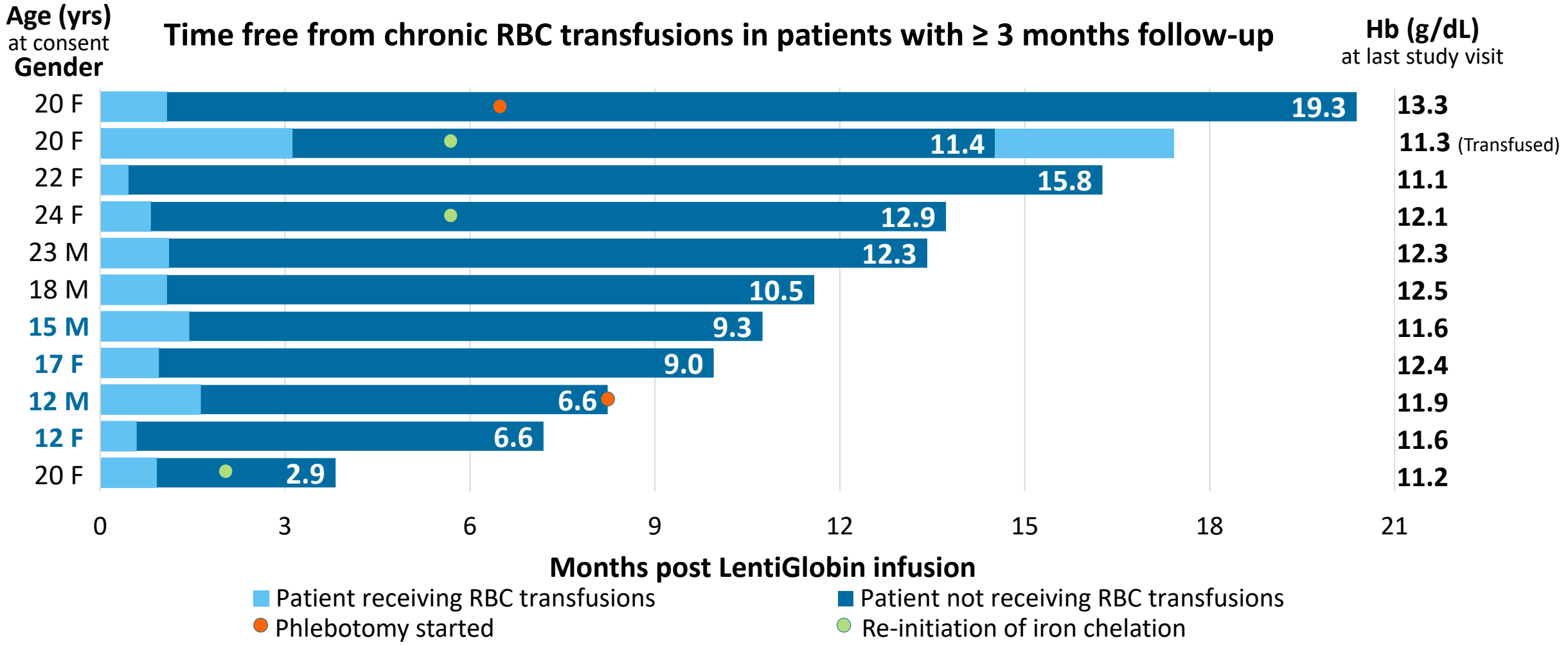




Patients re-initiated iron chelation therapy a median of 13 months after LentiGlobin infusion (min – max: 2 – 16 months)

Medians (Q1, Q3) depicted. LIC, liver iron concentration; TI, transfusion independence

HGB-207: 10/11 patients are transfusion free with Hb > 11 g/dL



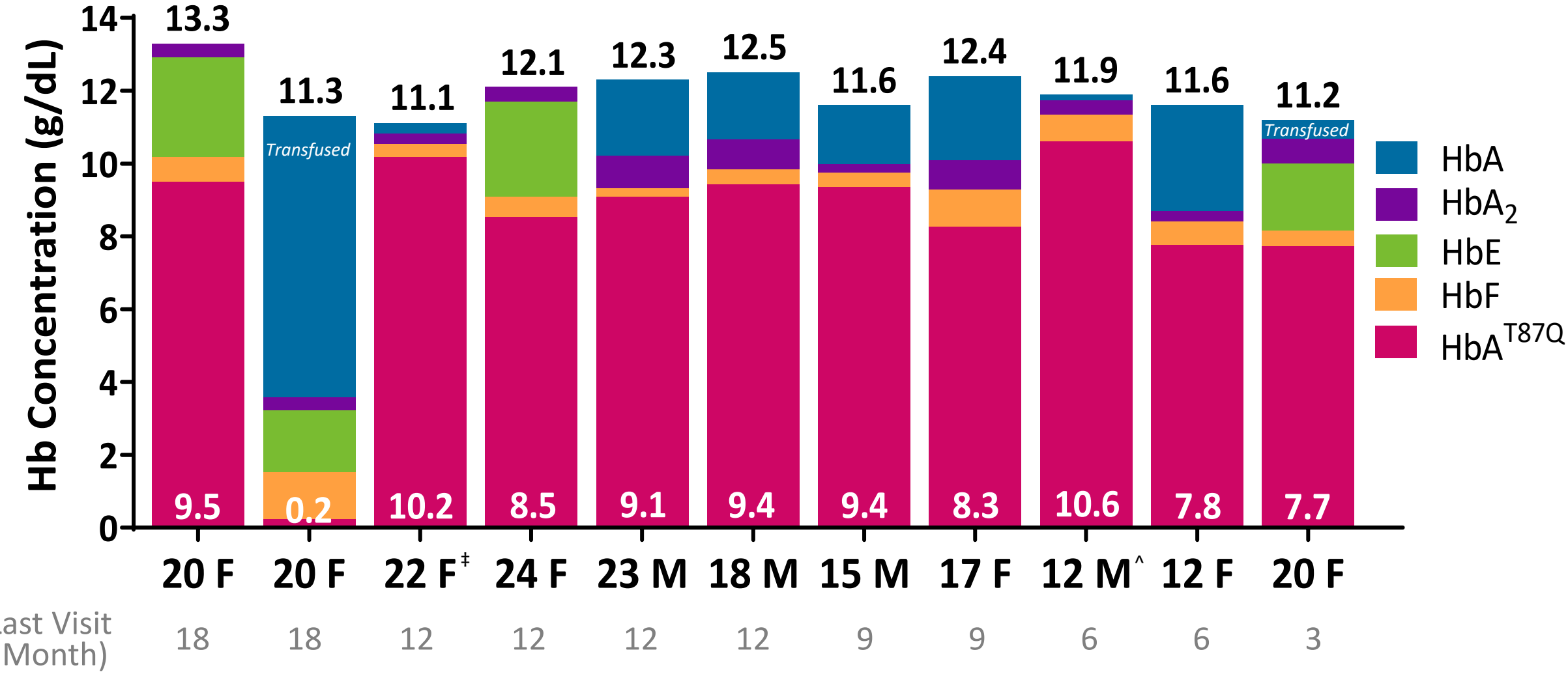
Patients 1 and 3 have achieved the protocol definition of transfusion independence

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

Hb, hemoglobin; RBC, red blood cell

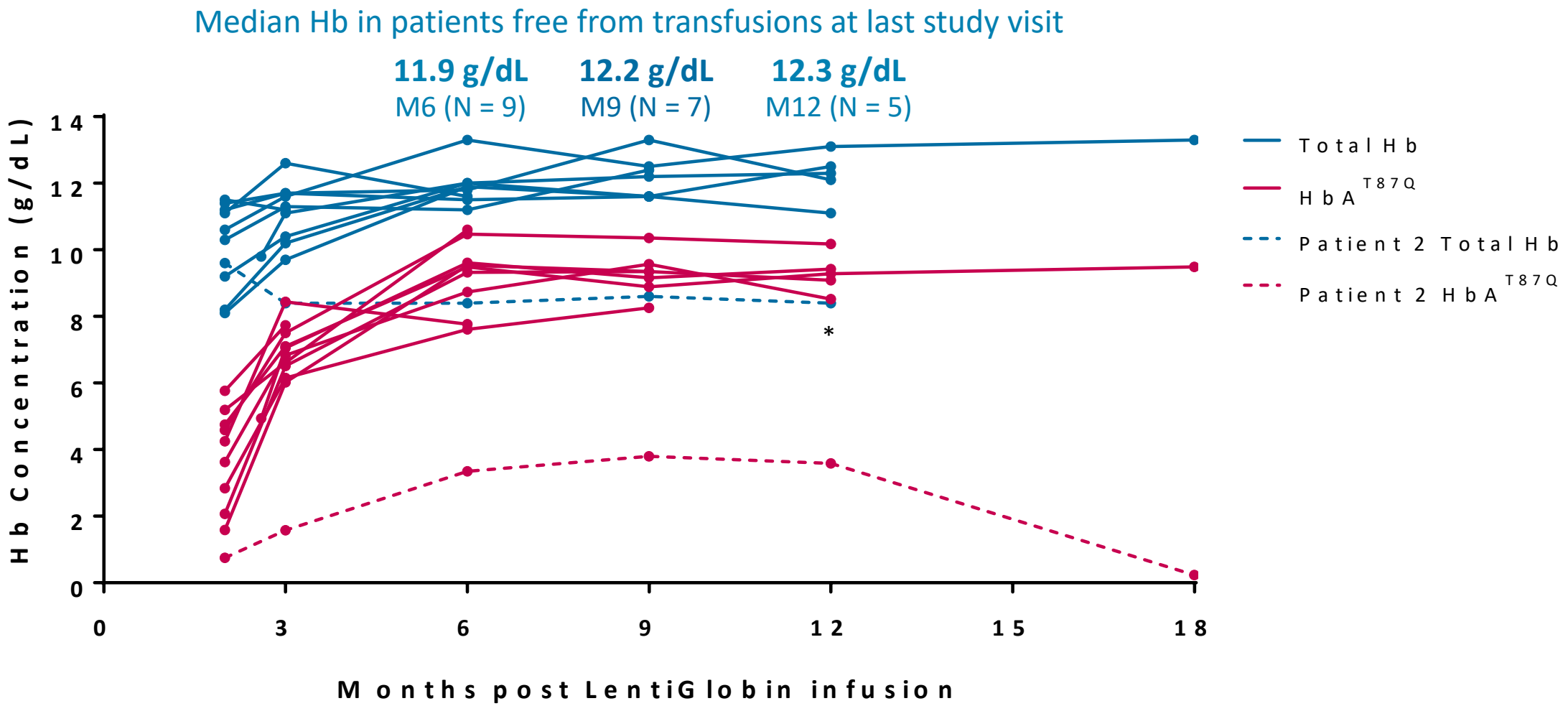
Data as of September 14, 2018

HGB-207: Gene therapy-derived HbA^{T87Q} significantly contributes to total Hb in 10/11 patients



‡Patient is homozygous for IVS-I-5 β-globin mutation; ^Patient is heterozygous for IVS-I-5 β-globin mutation. Hb, hemoglobin. Age is at time of at consent.

HGB-207: Total Hb and gene therapy-derived HbA^{T87Q} remain stable in patients free from transfusions

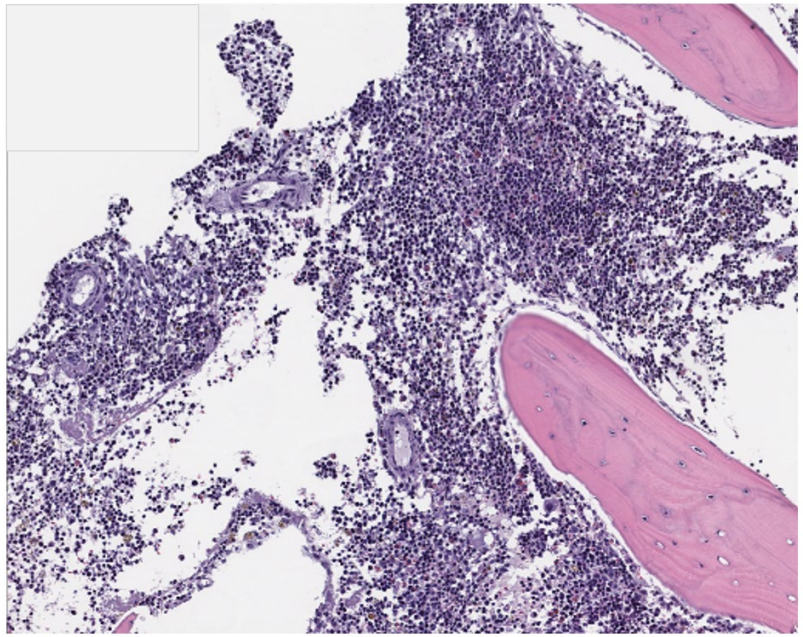


*Last Hb before patient restarted red blood cell transfusions; Hb, hemoglobin

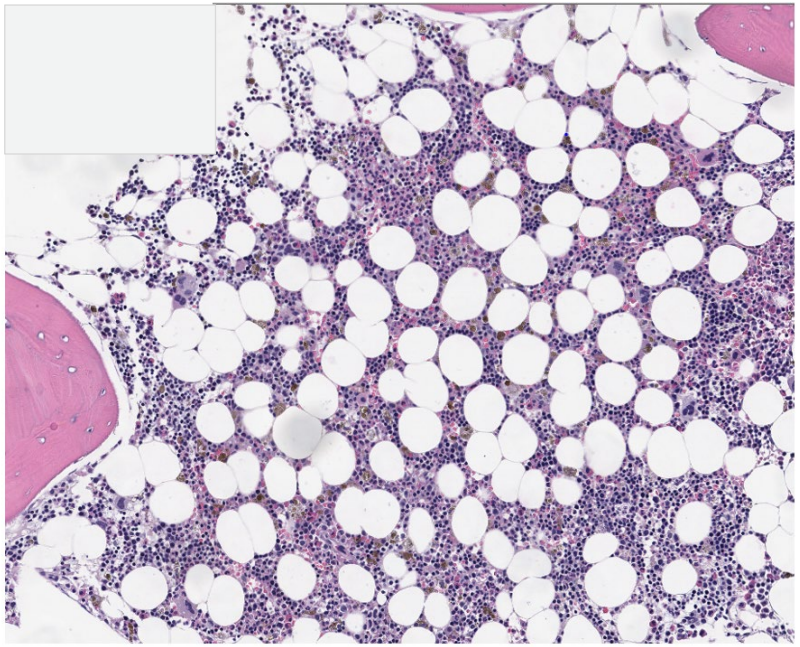
HGB-207: Improvement in erythropoiesis following LentiGlobin gene therapy

Patient 1 (20 yr old female) bone marrow analysis

Screening

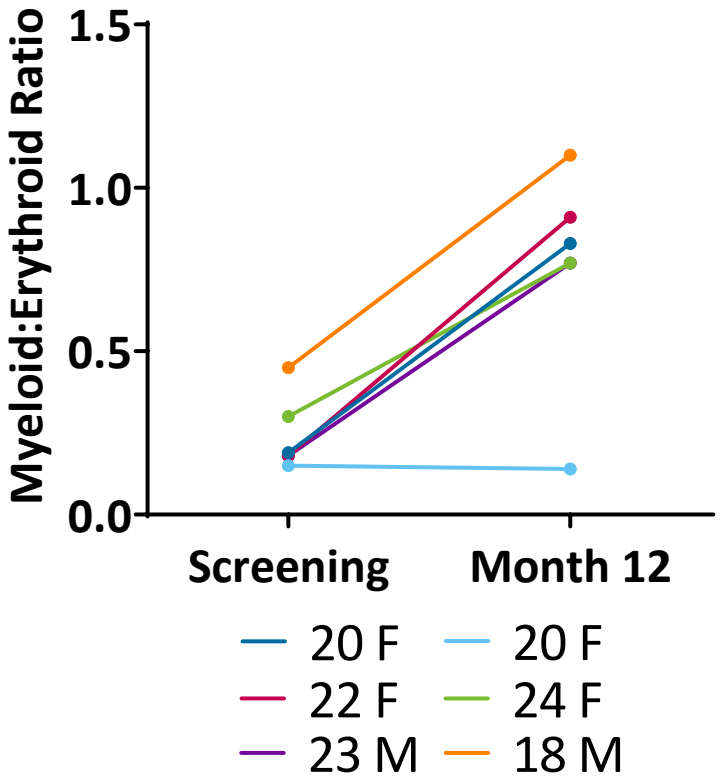


Month 12 post-LentiGlobin



Hb at Month 12: 13.1 g/dL

Myeloid:Erythroid ratio following LentiGlobin gene therapy



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

Hb, hemoglobin

1. Origa R. GeneReviews®. 2018.

HGB-204 and HGB-207: Safety profile in patients with non-β^0/β^0 genotypes

Non-hematologic* grade ≥ 3 AEs in ≥ 2 patients in HGB-207† LentiGlobin infusion to up to 2 years of follow-up	HGB-204 N=10 n (%)	HGB-207 N=16 n (%)
Stomatitis	8 (80)	9 (56)
Febrile neutropenia	6 (60)	4 (25)
Pharyngeal inflammation	2 (20)	2 (13)
Epistaxis	–	3 (19)
Pyrexia	–	3 (19)
Veno-occlusive liver disease	1 (10)	3 (19)
ALT increased	–	2 (13)
Bilirubin increased	–	2 (13)
Hypoxia	–	2 (13)

- **One grade ≥ 3 AE was considered possibly related to LentiGlobin**
  - Grade 3 thrombocytopenia in HGB-207
- **No deaths or graft failure**
- **No vector-mediated replication-competent lentivirus**
- **No evidence of clonal dominance**

Serious veno-occlusive liver disease

- HGB-204: 2 grade 3 serious VODs
  - One in a non-β^0/β^0 patient, one in a β^0/β^0 patient
  - Baseline LIC 8.4 and 10.4 mg/g
- HGB-207: 3 grade 4 serious VODs
  - Baseline LIC 1.0, 5.6, 8.5 mg/g
- All events resolved following defibrotide

*Hematologic AEs commonly observed post-transplant have been excluded. †In HGB-204, non-hematologic grade ≥ 3 AEs also included 3/10 (30%) patients with irregular menstruation.
AE, adverse event; ALT, alanine aminotransferase; VOD, veno-occlusive liver disease

Summary of LentiGlobin gene therapy in patients with transfusion-dependent β-thalassemia with non-β^0/β^0 genotypes

HGB-204

- 80% (8/10) patients have achieved durable transfusion independence with up to 4 years follow-up

HGB-207

- 2/3 patients with sufficient follow-up have achieved the primary endpoint of transfusion independence with up to 20 months follow-up
- 10/11 patients with ≥ 3 months follow-up have stopped RBC transfusions
- Bone marrow morphology indicates improvements in erythropoiesis

Safety

- The safety profile remains generally consistent with myeloablative busulfan conditioning
  - Including serious AEs of veno-occlusive liver disease
- Some patients experienced delayed platelet engraftment
  - Median day of platelet engraftment after DP infusion: 50.5 and 44.5 days in HGB-204 and HGB-207, respectively
- No deaths, graft-failure, vector-mediated replication-competent lentivirus, or clonal expansion observed to date

AE, adverse event; DP, drug product; RBC, red blood cell

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bluebird bio, Inc.:

- Dana Martin
- Kailey Walsh
- Sarah Hunter
- Alexandria Petrusich
- Marisa Gayron
- Jun Yu
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