Long term clinical outcomes of LentiGlobin gene therapy for transfusion-Dependent β-thalassemia in the Northstar (HGB-204) study

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Northstar (HGB-204) study

Phase 1/2 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 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 cell

Data as of 13 December 2018

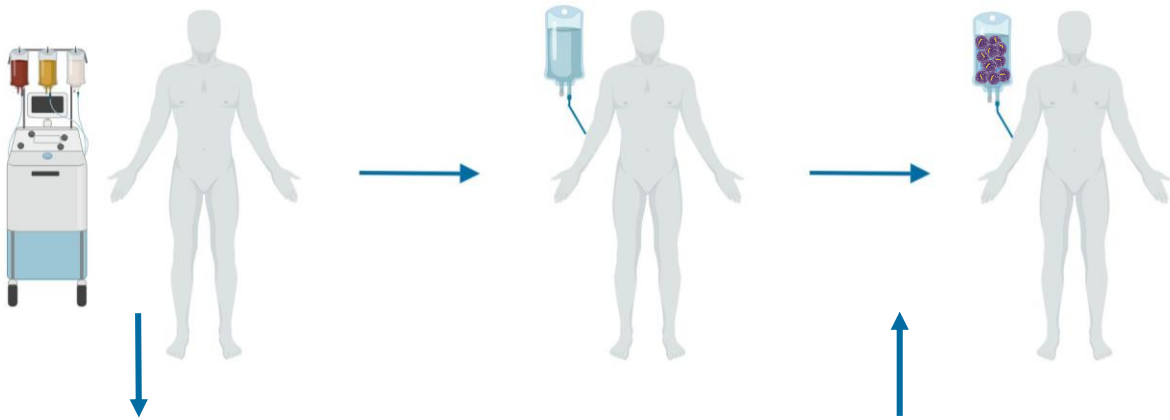
HGB-204: Study design

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

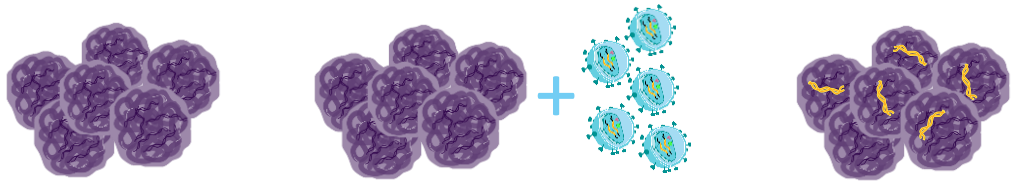
Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and reconstitute functional RBCs



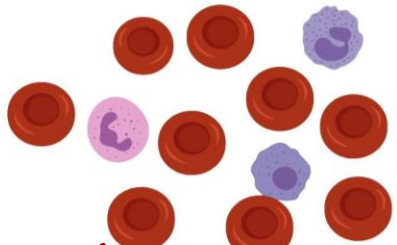
LentiGlobin centralized manufacturing



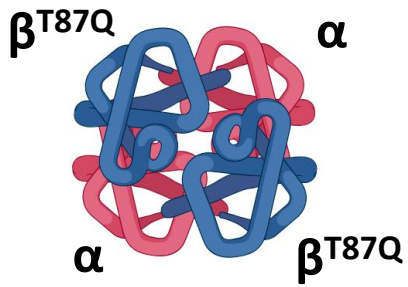
Select CD34+ cells

Transduce with BB305 lentiviral vector

Cryopreserve, test, release DP



Gene therapy-derived HbA^{T87Q}



2-year Follow-up

Long-term Follow-up Study

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

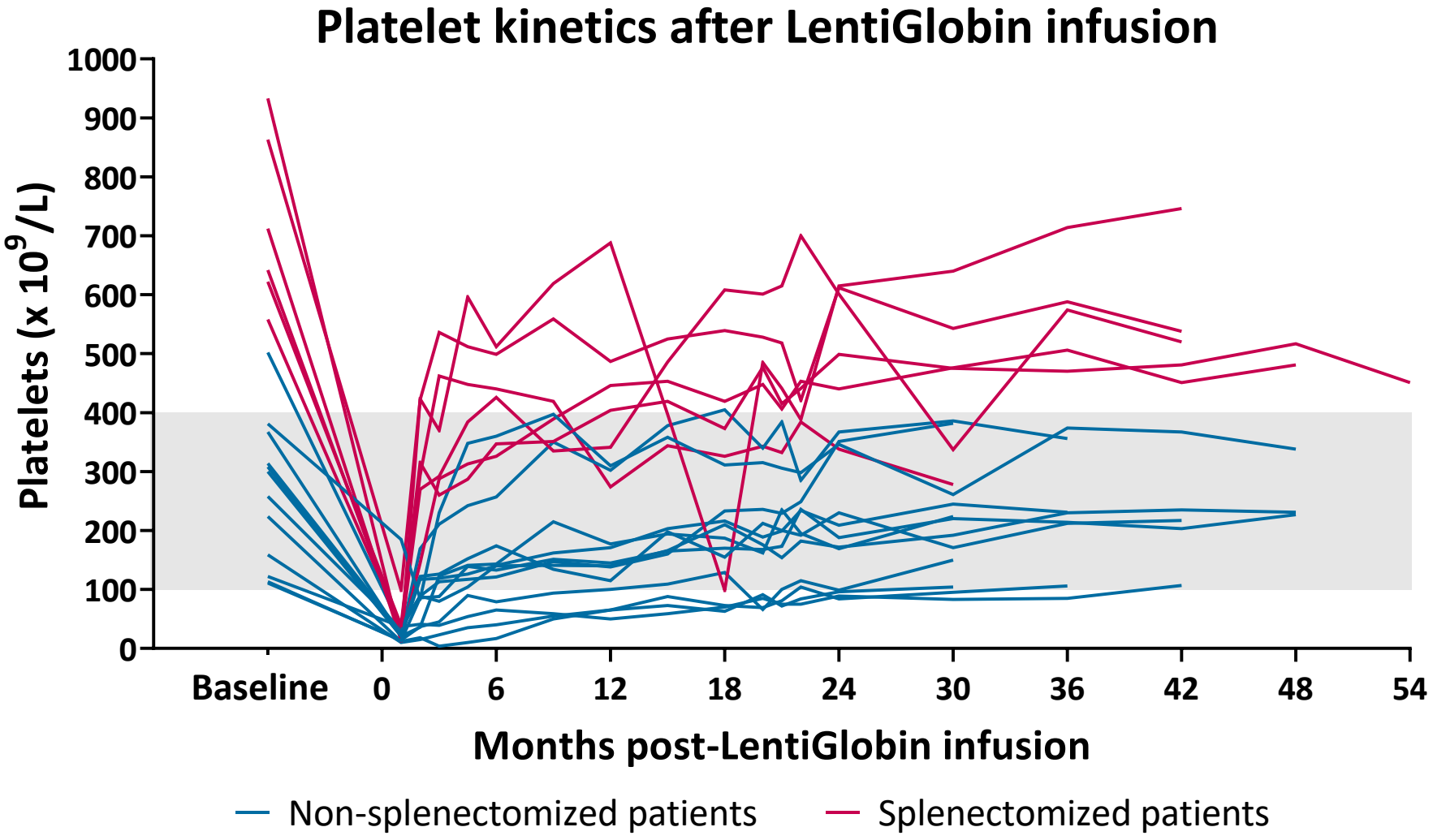
HGB-204: Patient and drug product characteristics

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

Drug Product Characteristics *per patient*	N = 18 median (min – max)
Drug product cell dose $x10^6$ CD34+ cells/kg	**8.1** (5.2 – 18.1)
Drug product VCN vector copies/diploid genome	**0.7** (0.3 – 1.5)
CD34+ cells transduced %	**31.5** (17 – 58)
Treatment Characteristics	
Neutrophil engraftment ANC ≥ 500 cells/μL x 3 days, days	**18.5** (14 – 30)
Platelet engraftment Platelets ≥ 20,000 cells/μL, days	**39.5** (19 – 191)

ANC, absolute neutrophil count; RBC, red blood cell; VCN, vector copy number

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



Bleeding AEs

- Grade ≥ 3 bleeding AEs from LentiGlobin infusion to platelet engraftment:
  - Epistaxis (grade 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

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

Nonhematologic* grade ≥ 3† AEs reported in ≥ 2 patients *LentiGlobin infusion to 2 years' follow-up*	**N = 18** **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 *LentiGlobin infusion to last follow-up*	
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

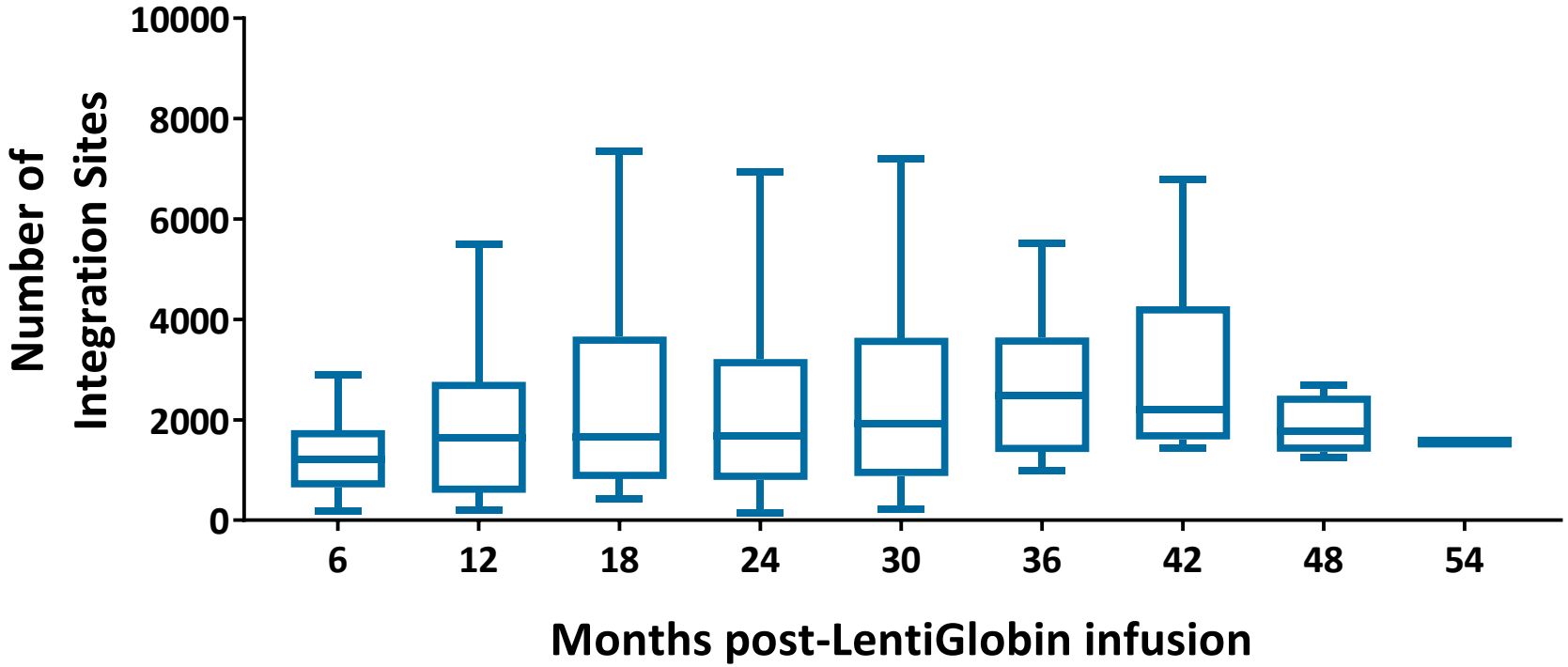
*Hematologic AEs commonly observed post-transplantation have been excluded; †No grade 4 or 5 non-hematologic AEs were reported;
‡Both VODs were grade 3 and serious; §Included 1 vena cava thrombosis and 1 intracardiac thrombus.

AE, adverse event

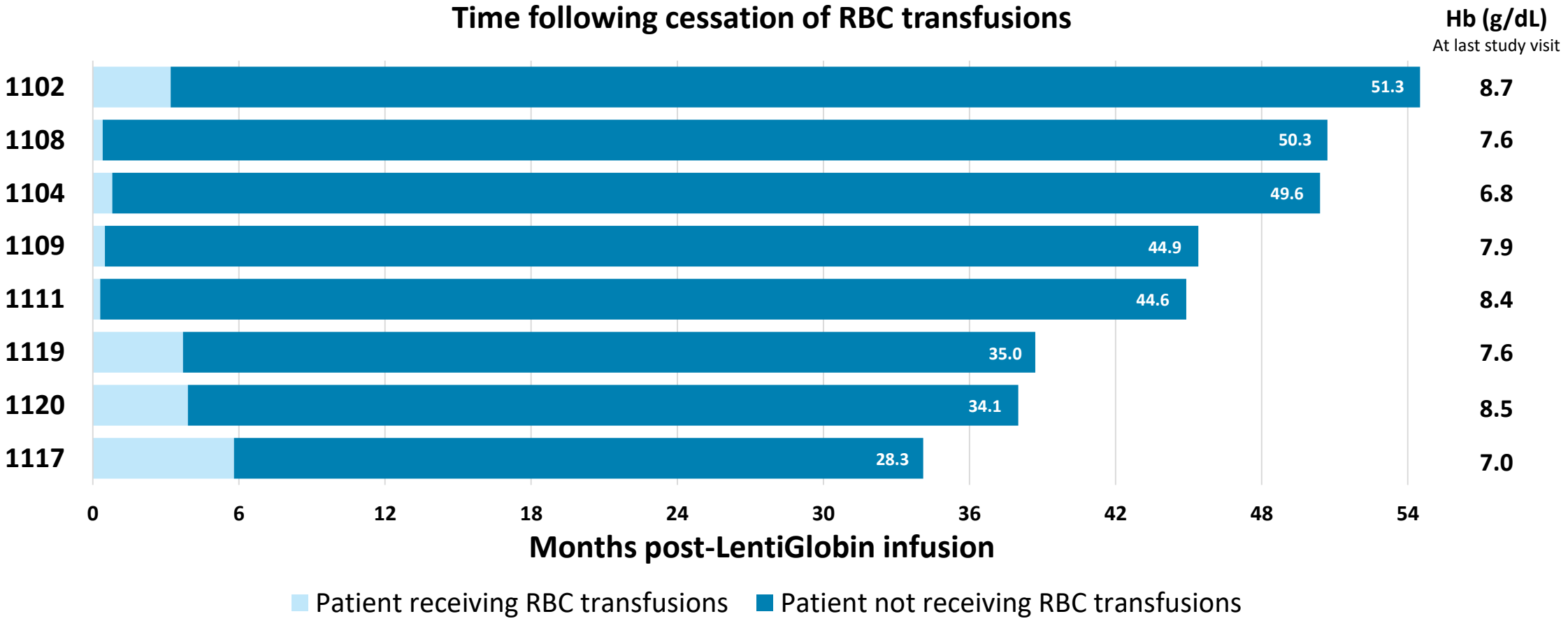
HGB-204: Vector integration profile is polyclonal over time

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

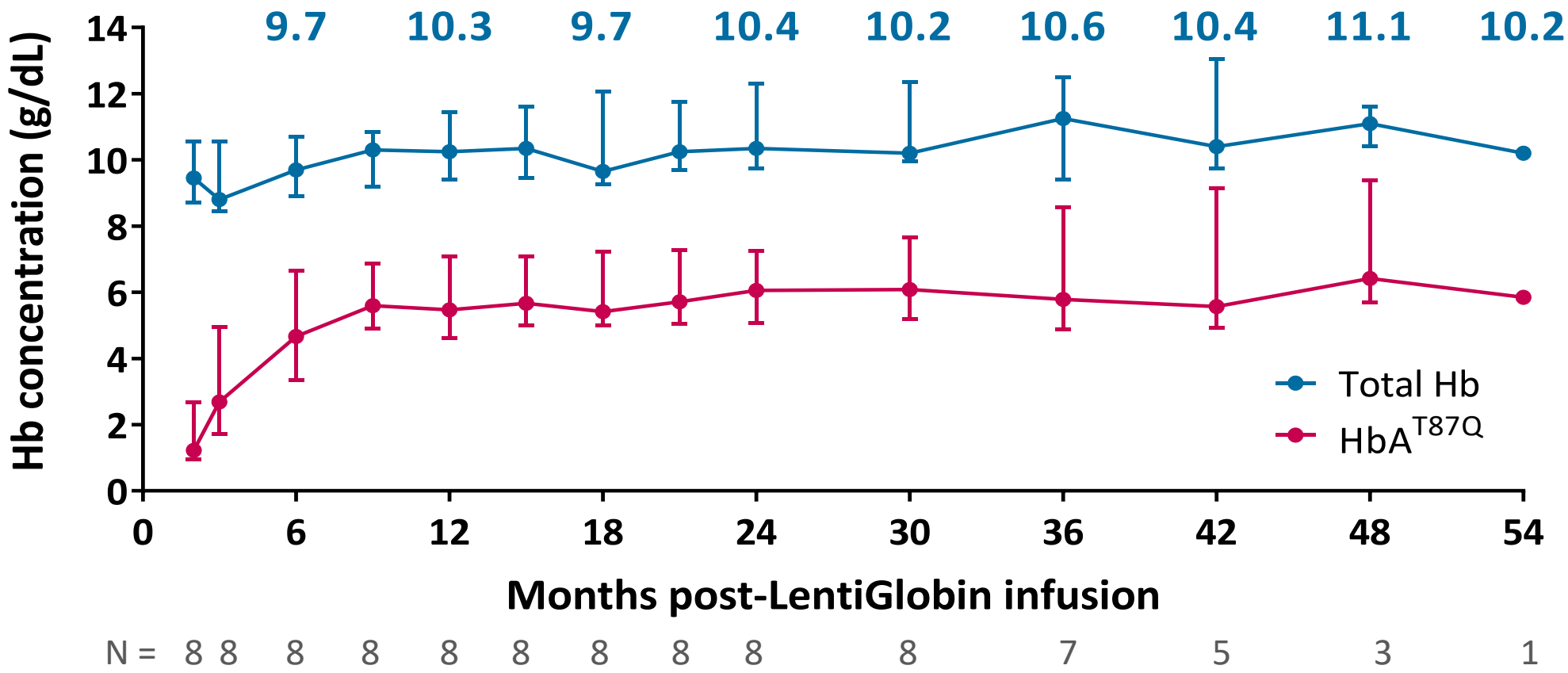


Median duration of TI: 44.8 months (min – max: 28.3 – 51.3 months); responses are ongoing
Median weighted average Hb during TI: 10.3 g/dL (min – max: 9.3 – 13.3 g/dL)

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

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

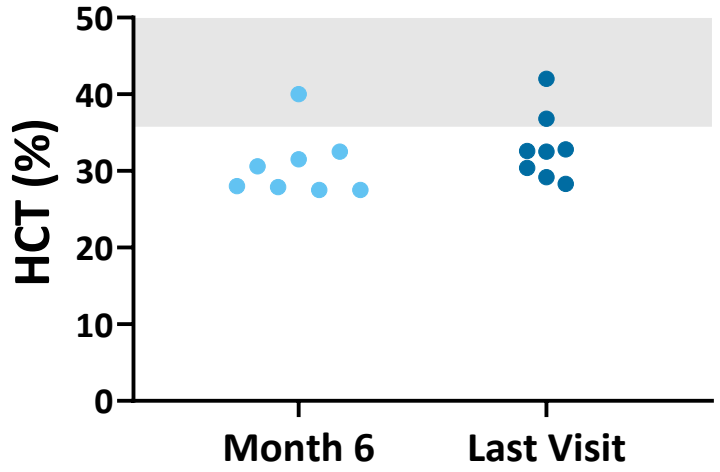


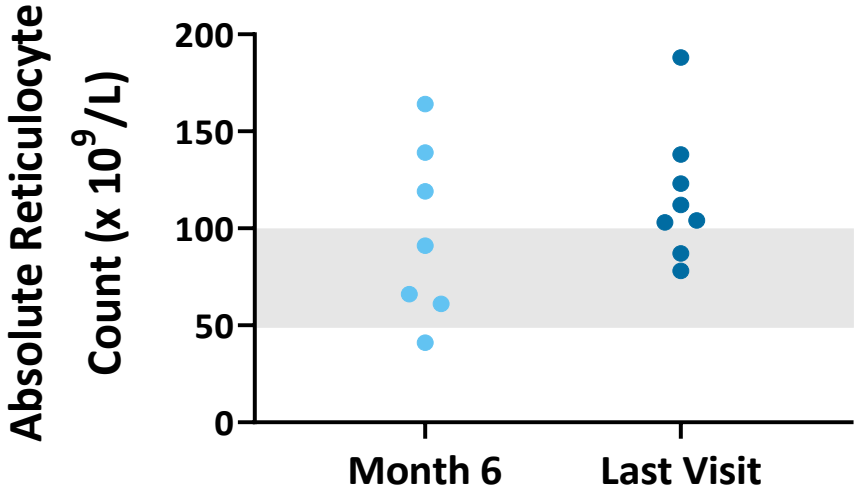
Medians (Q1, Q3) depicted.

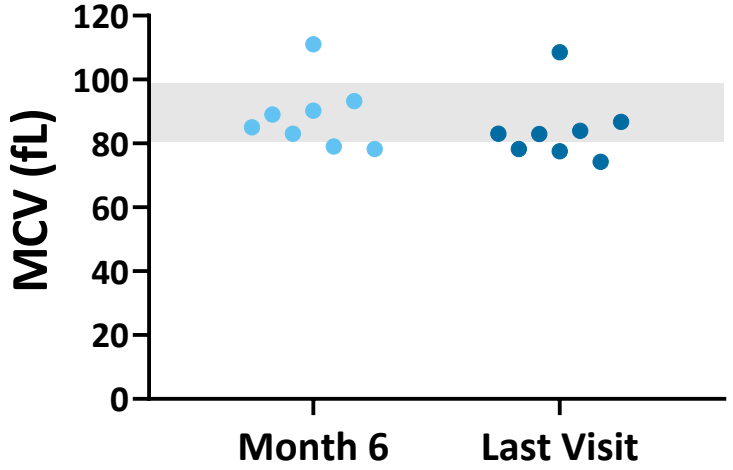
Hb, hemoglobin

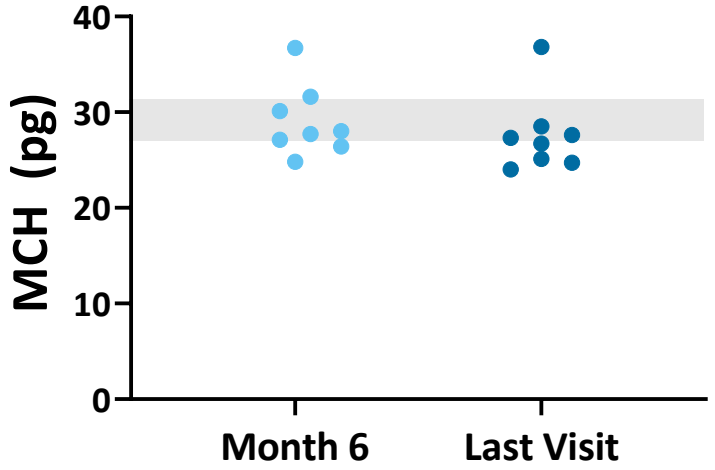
HGB-204: RBC indices were generally normal with transfusion independence

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





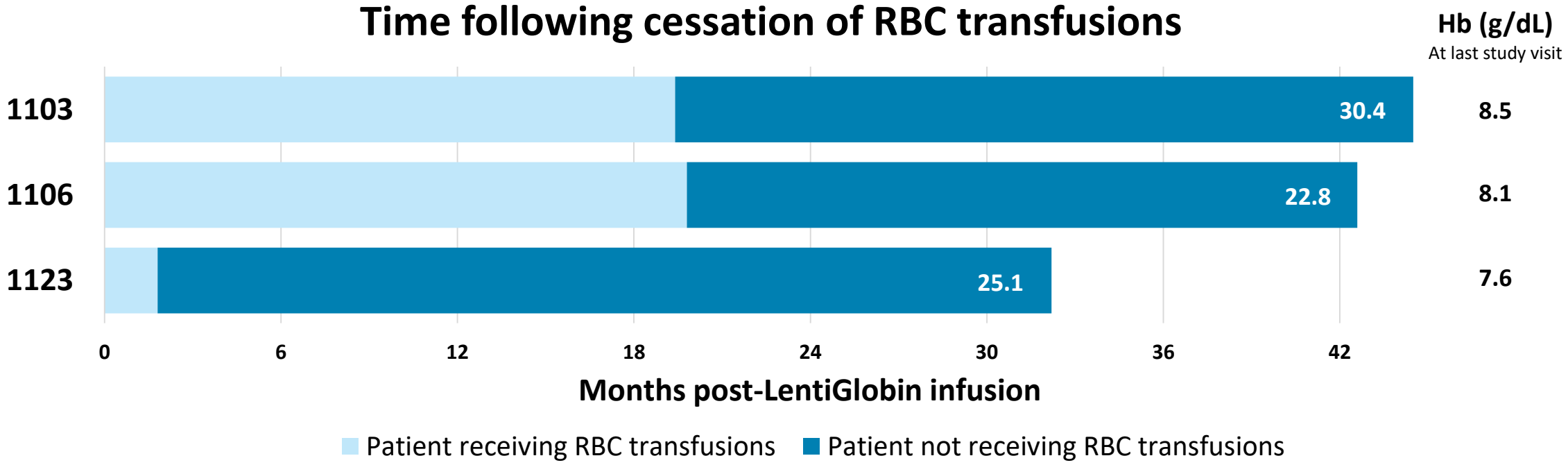




Last visit ranges from Month 36 to Month 54 post-LentiGlobin infusion. Gray bar indicates reference range.

HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood cell

HGB-204: 3/8 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: 25.1 months (min – max: 22.8 – 30.4 months)

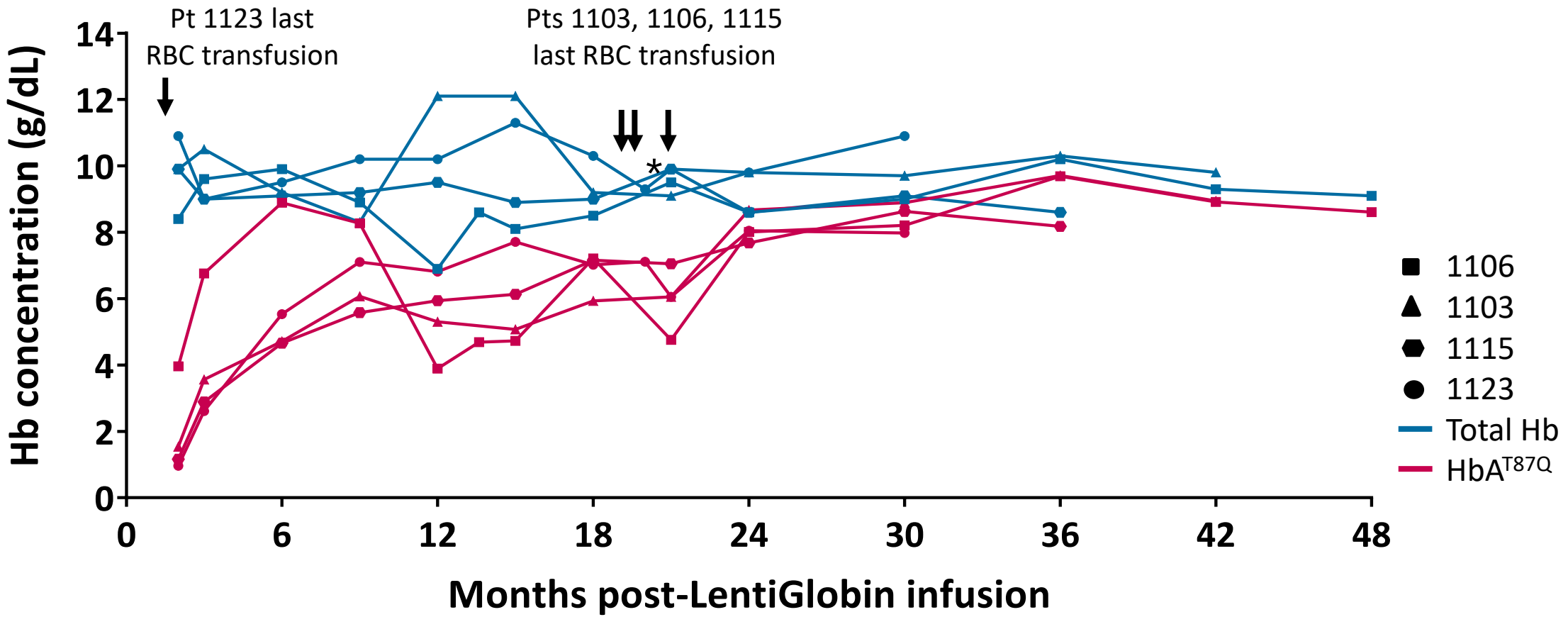
Median weighted average Hb during TI: 9.9 g/dL (min – max: 9.9 – 10 g/dL)

*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

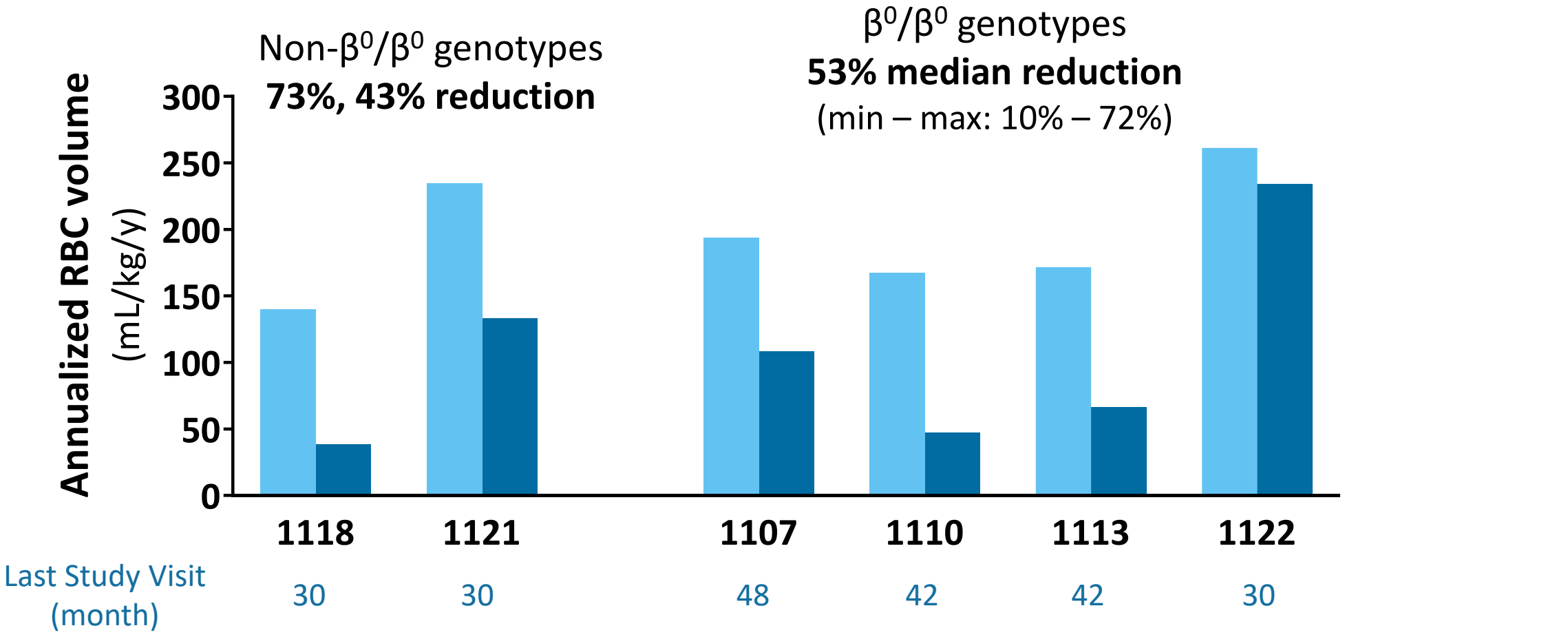
Hb in patients with β^0/β^0 genotypes who have been transfusion-free for > 12 months



*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

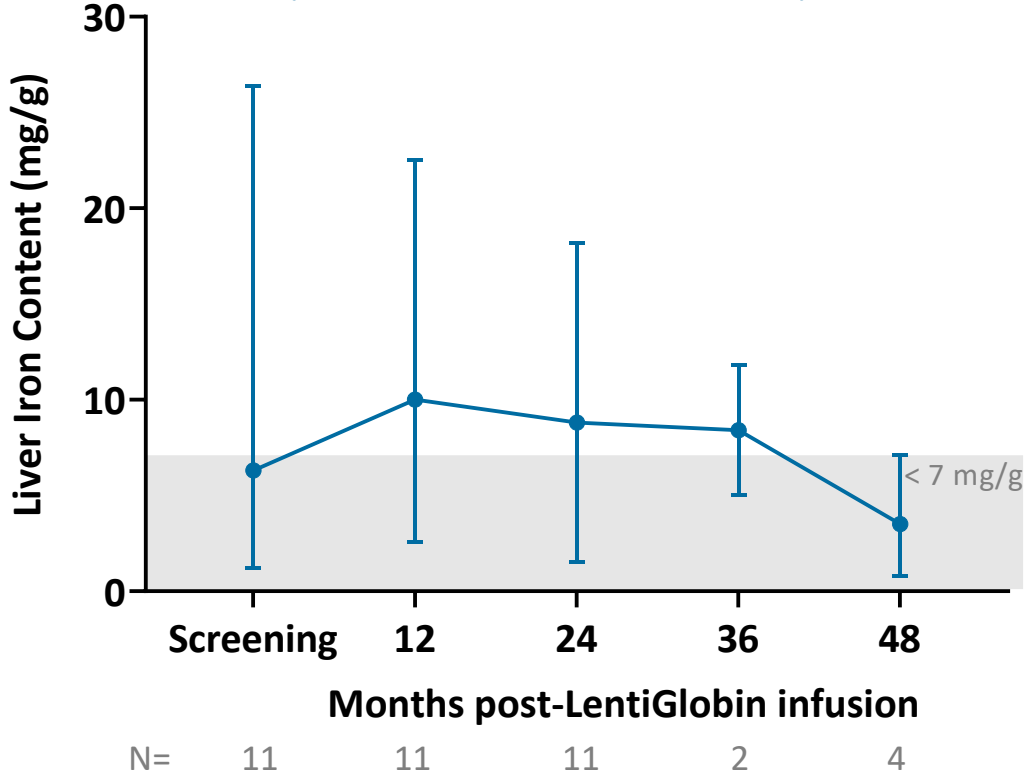


DP, drug product; RBC, red blood cell

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

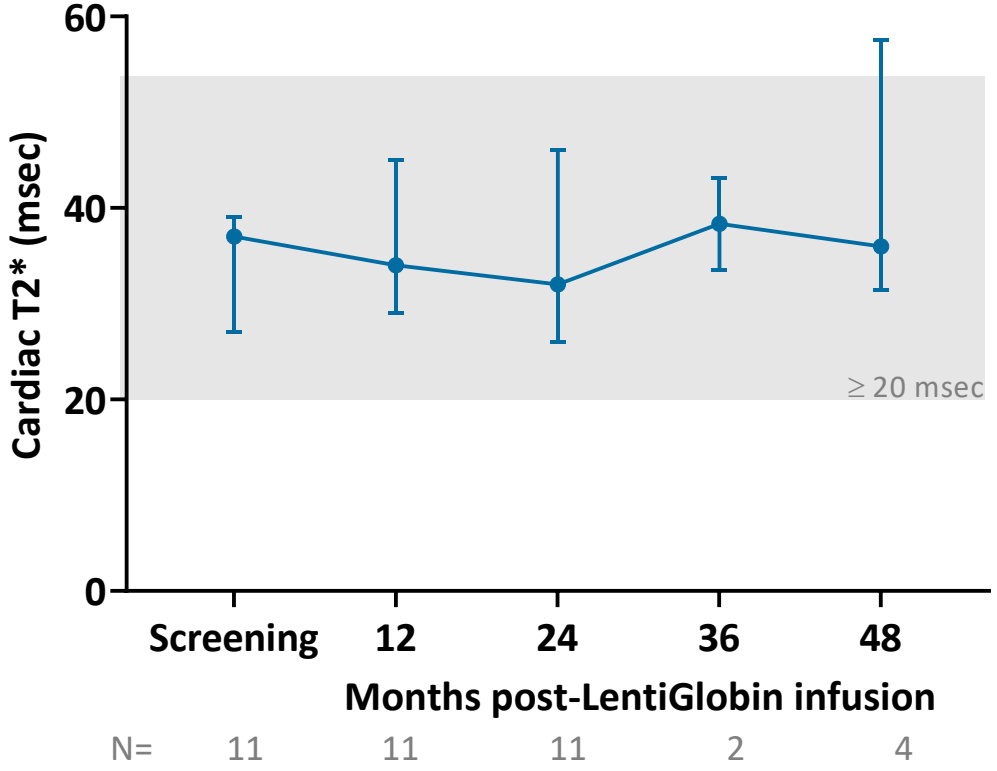
(min – max: 38% – 83%; N = 4)



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)

Medians (min, max) depicted. LIC, liver iron concentration; M, month

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 7.0 – 8.7 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 that of myeloablative conditioning
  - Some patients had delayed platelet engraftment, but no serious bleeding events

Hb, hemoglobin; LIC, liver iron concentration; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia

Data as of 12 June 2019

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