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Efficacy and safety of LentiGlobin gene therapy in patients with transfusion-dependent β-thalassaemia and non-β^0/β^0 genotypes: Updated results from the completed phase 1/2 Northstar and ongoing phase 3 Northstar-2 studies

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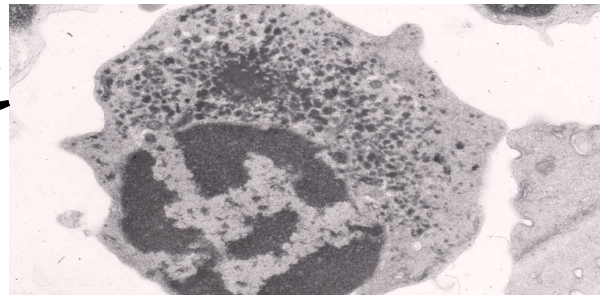
β-Thalassaemia Pathophysiology



Decreased β globin synthesis
Unpaired α Globin

Splenomegaly

Haemolysis

Ineffective erythropoiesis

Anaemia

Transfusion

Erythropoietin

Erythroid marrow expansion

Skeletal deformities, osteopenia

Iron absorption

Iron overload

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, haemoglobin

Data as of 14 September 2018

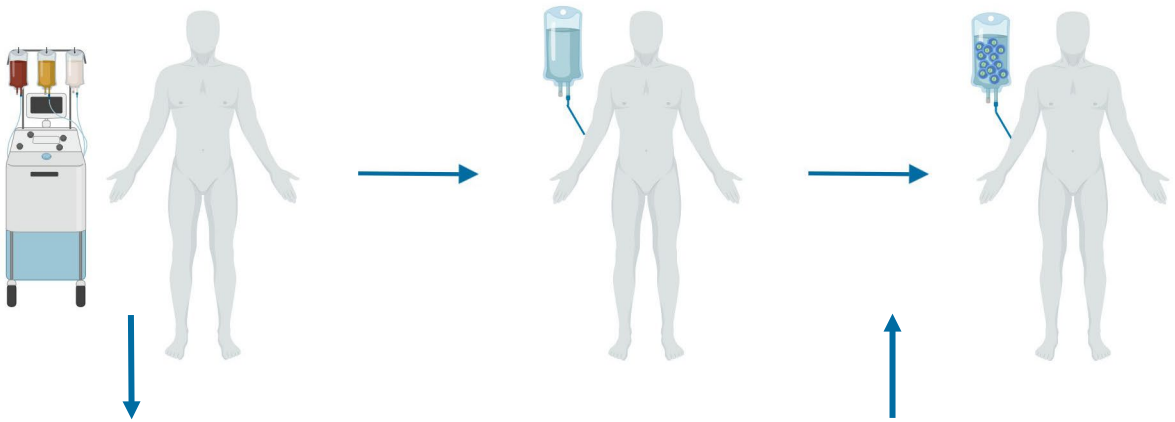
HGB-204 and HGB-207: Study design

HSC collection
Mobilisation (G-CSF + plerixafor) & aphaeresis

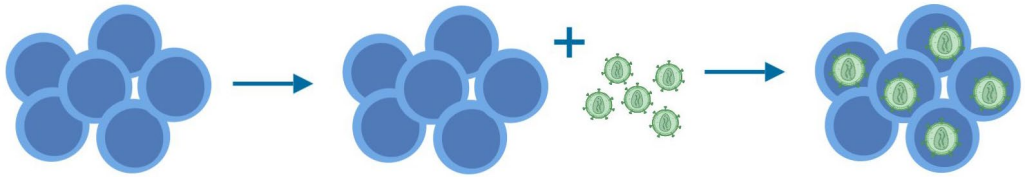
Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs



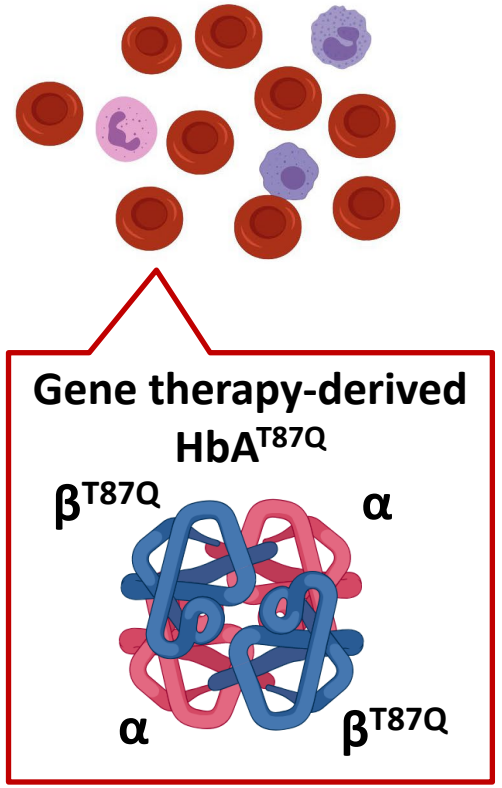
LentiGlobin DP centralised manufacturing
Refined manufacturing process used in HGB-207



Select CD34+ cells

Transduce with BB305 lentiviral vector

Cryopreserve, test, release DP



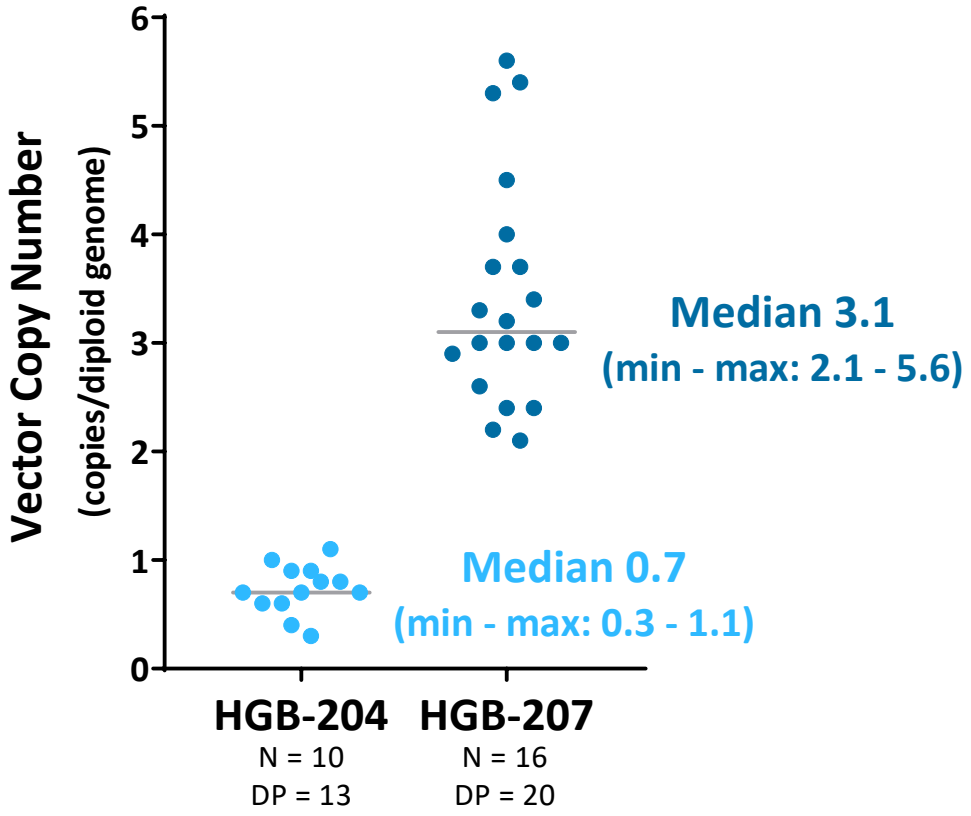
2-yr follow-up

Long-Term Follow-Up Study

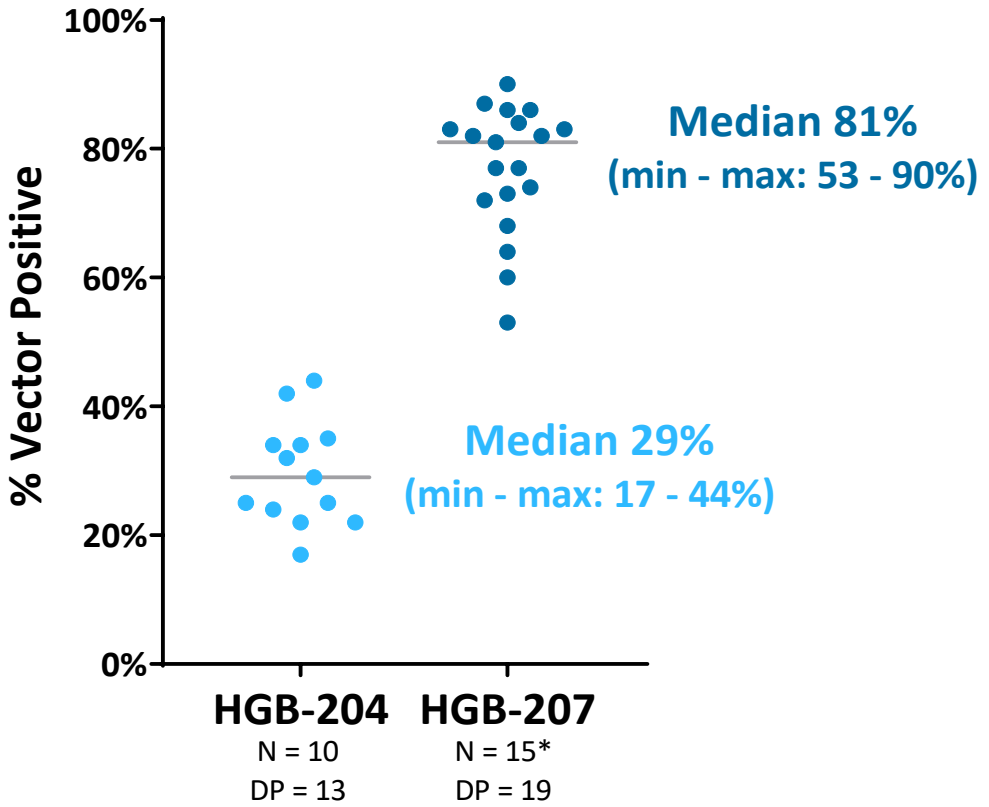
DP, drug product; G-CSF, granulocyte colony-stimulating factor; HSC, haematopoietic stem cell; RBC, red blood cell

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 mobilised 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)
Pre-study pRBC transfusion volume annualised 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)
Cardiac T2* median (min – max), msec		**37.5** (27 – 54)	**36.5** (20.6 – 50.9)
Splenectomy, n, %		**3** (30)	**4** (25)

Treatment Characteristics

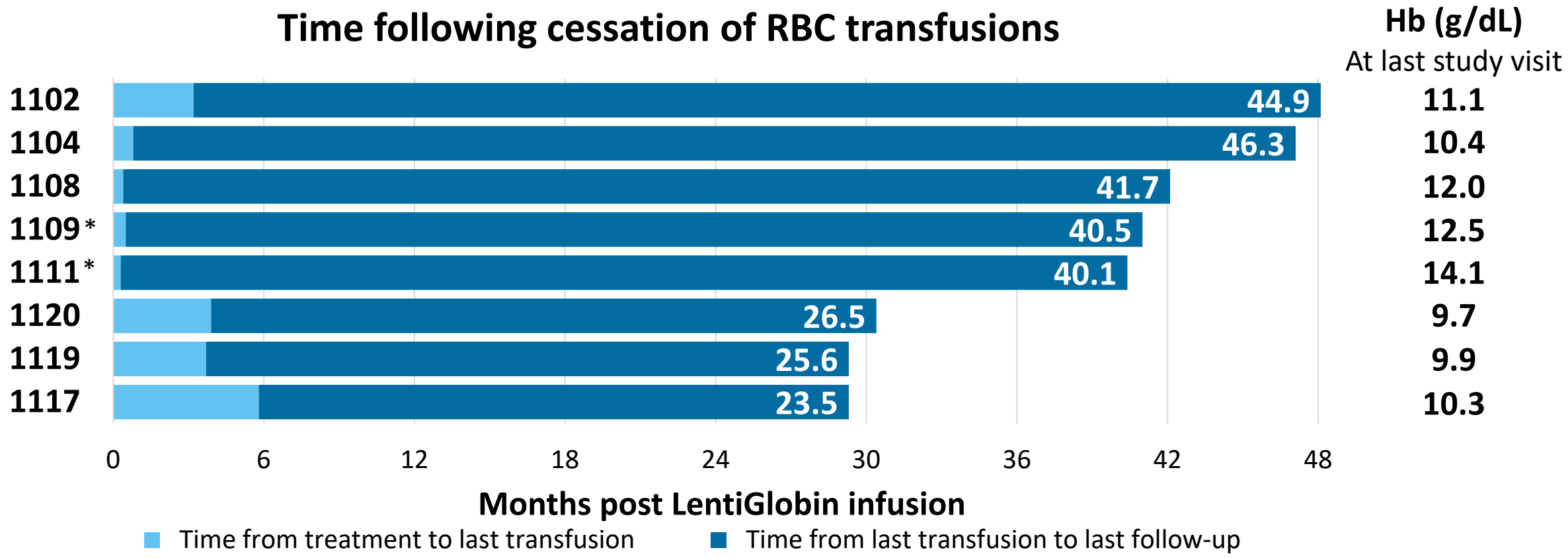
	HGB-204 (N = 10) median (min – max)	HGB-207 (N = 16) median (min – max)
Busulfan AUC estimated average x 4 days, µM*min	**4060** (3030 – 4417) *Target AUC: 4000 (3600 – 5000)*	**4545** (3709 – 8947) *Target AUC:† 4200 (3800 – 4500)*
Neutrophil engraftment ANC ≥ 500 cells/µL x 3 days, days	**18.5** (14 – 27)	**19**§ (13 – 32)
Platelet engraftment platelets >20k/µL, days	**50.5** (19 – 191)	**44.5**§ (20 – 84)

†Pre-protocol amendment, target busulfan AUC was 4500 (min – max: 4000 – 5000) µM*min.

§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

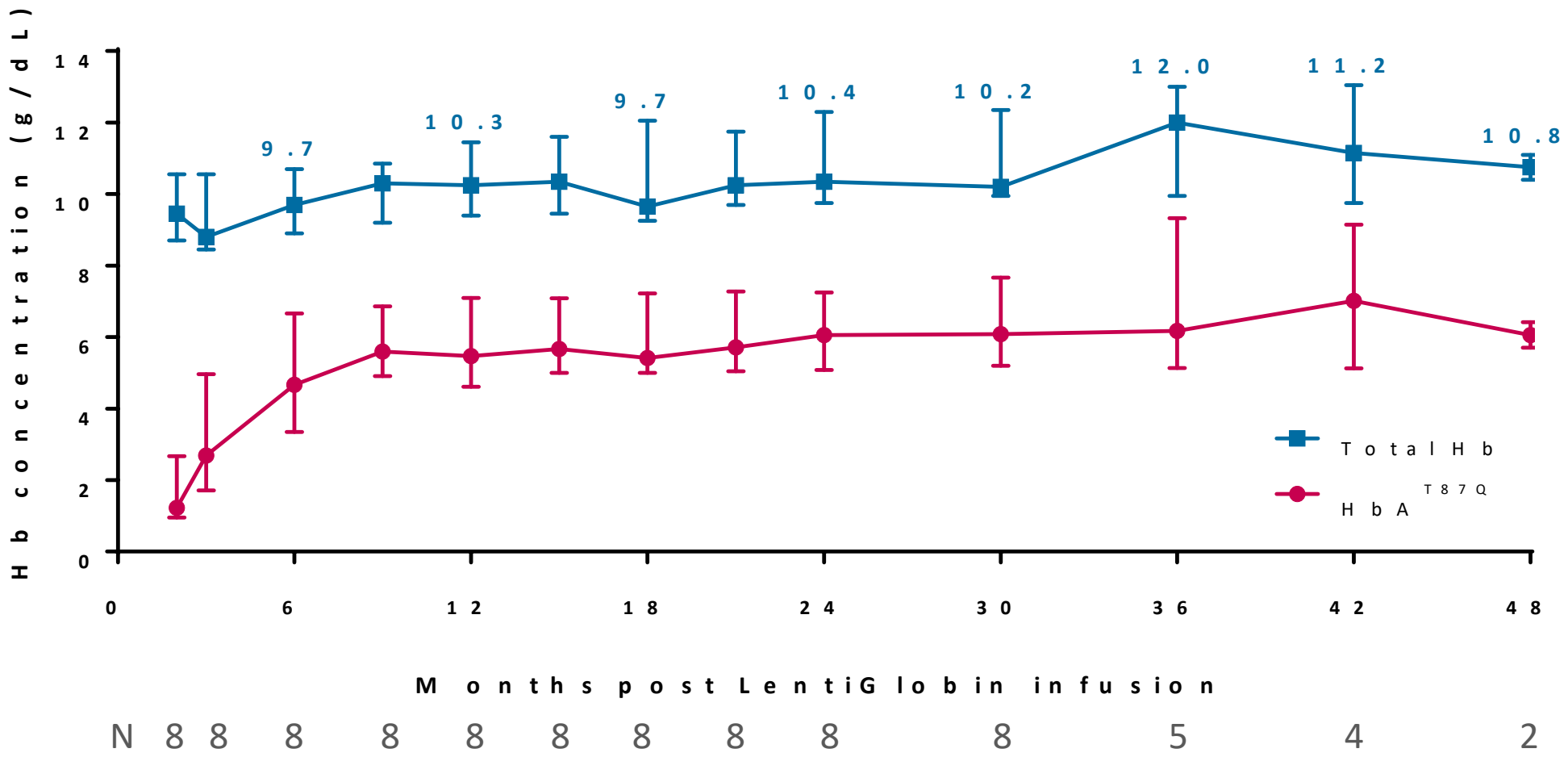


Median duration of TI: 38.0 months (min – max: 21.2 – 43.6 months)
Median weighted average Hb during TI: 10.2 g/dL (min – max: 9.3 – 13.2 g/dL)

*Indicates male patients. Hb, haemoglobin; 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

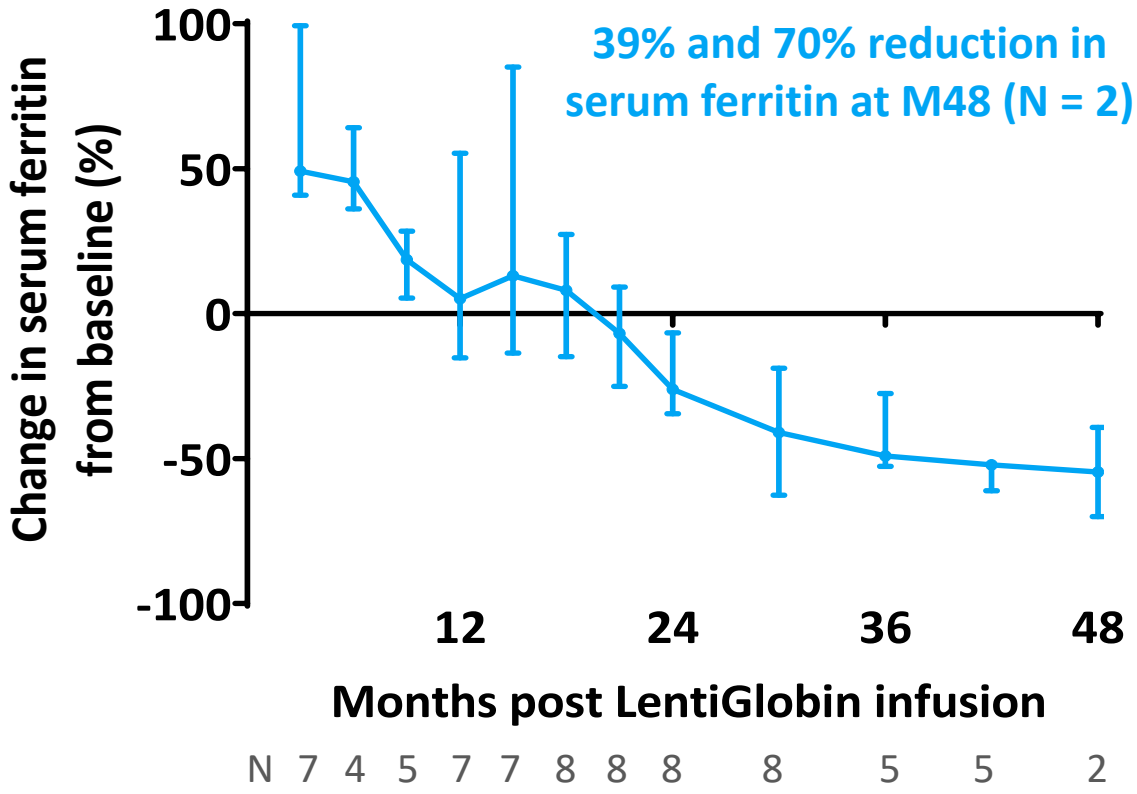
Median Hb in patients with non-β^0/β^0 genotypes who achieved transfusion independence

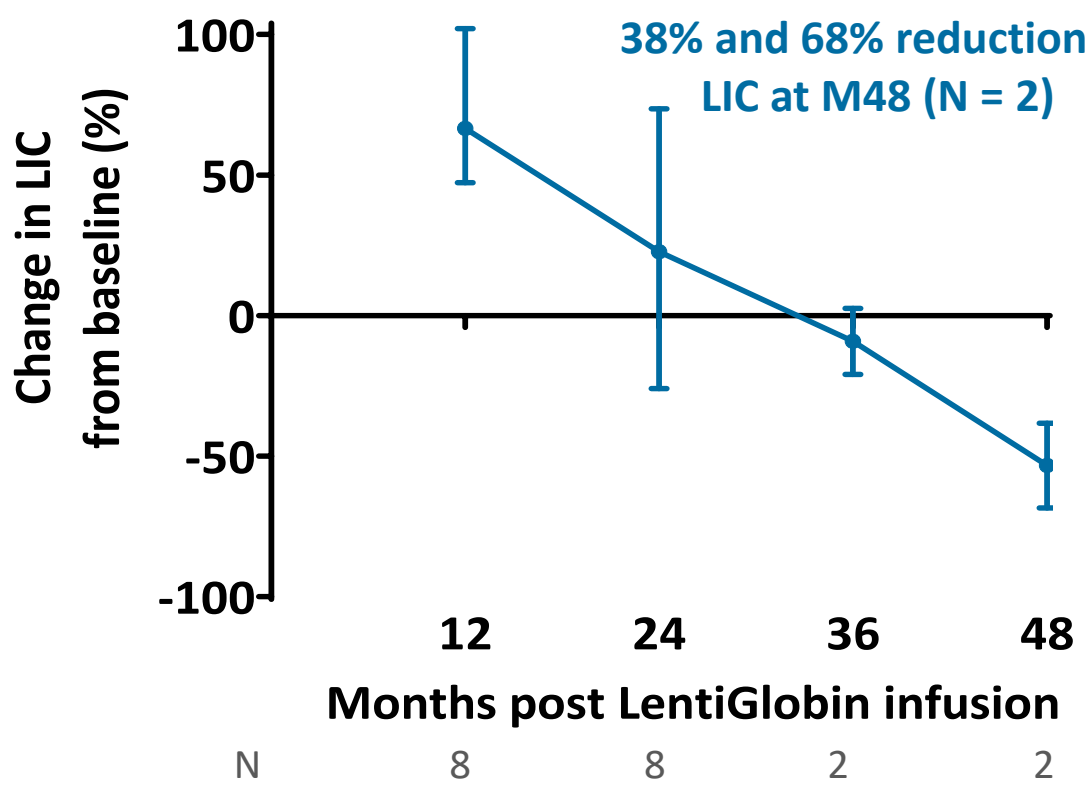


Medians (Q1, Q3) depicted; Hb, haemoglobin

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

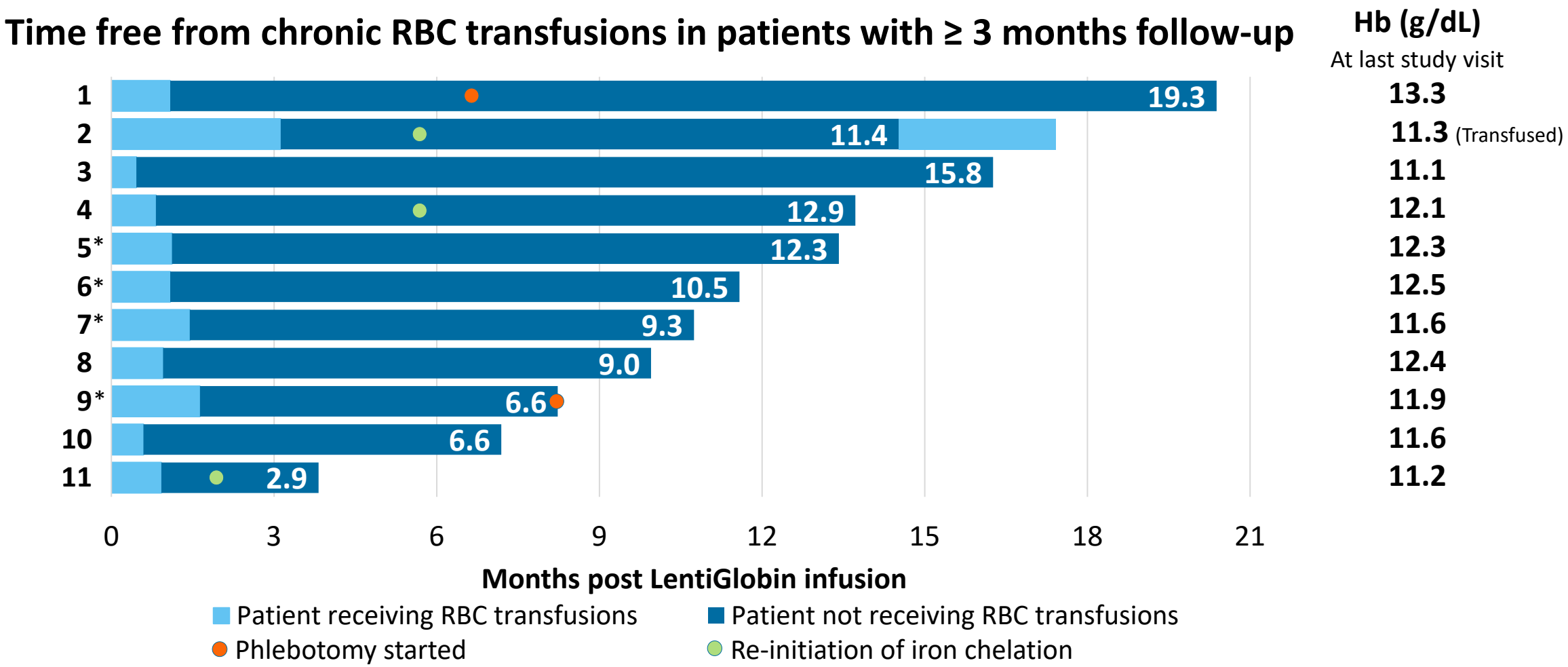




Patients re-initiated iron chelation therapy a median of 13 months after LentiGlobin infusion (min – max: 2 – 16 months)

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

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



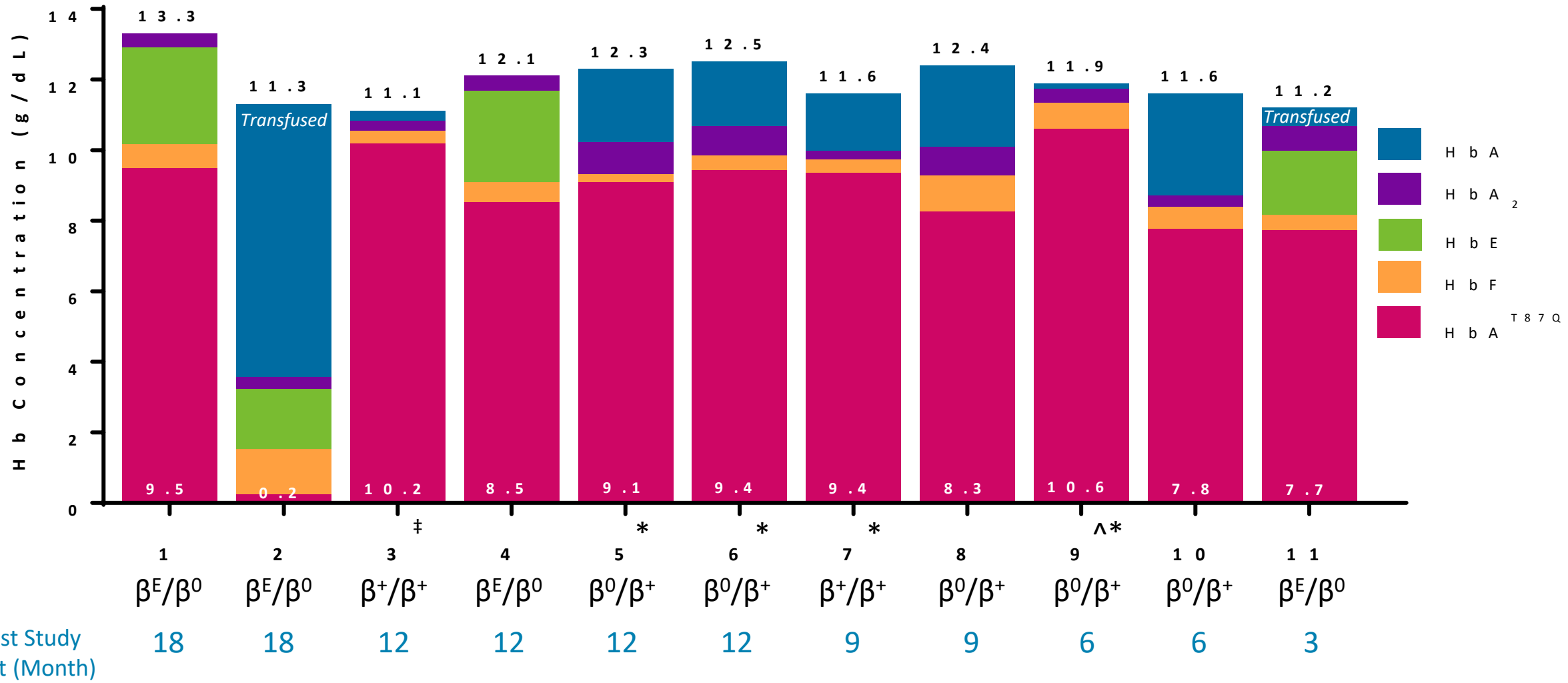
Patients 1 and 3 have achieved the protocol definition of transfusion independence

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

*Male patients; Hb, haemoglobin; RBC, red blood cell

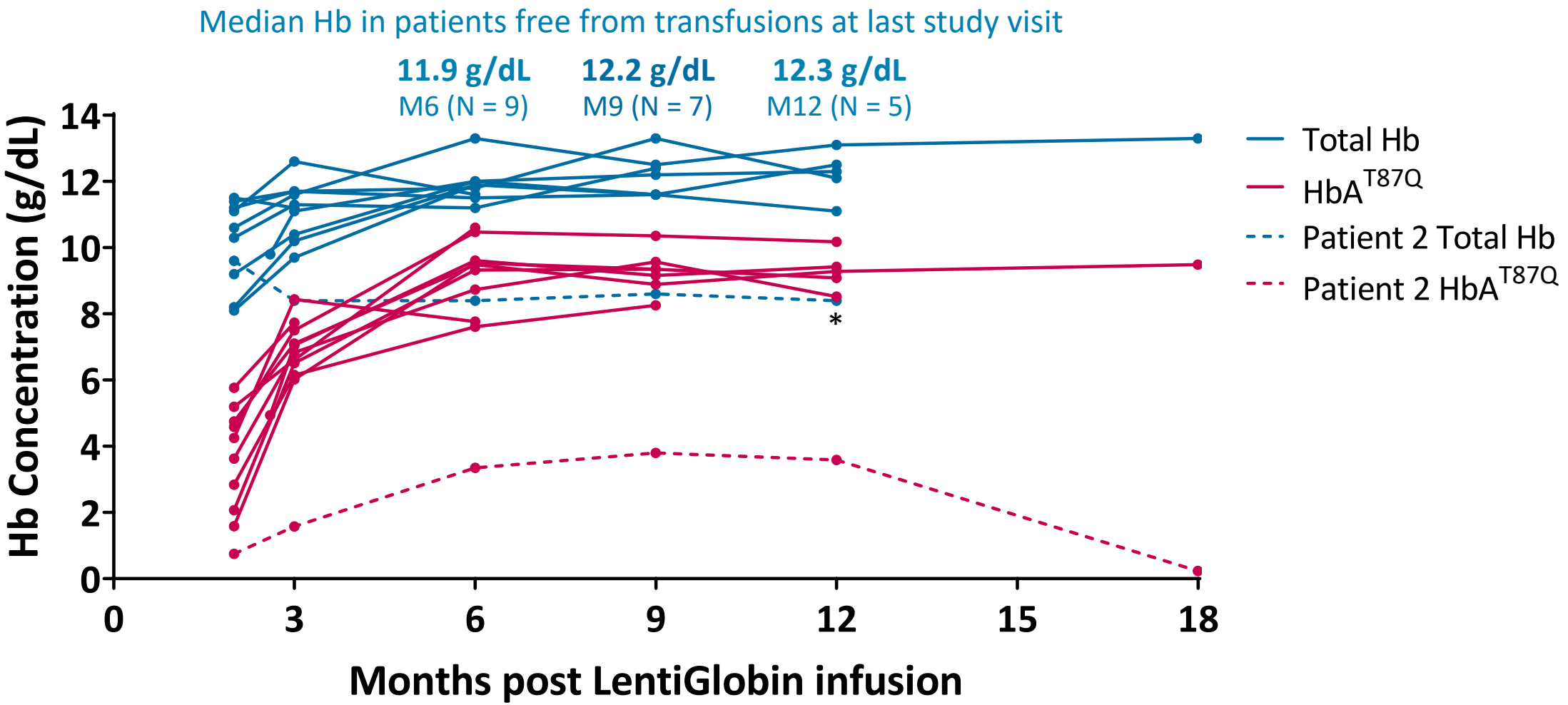
Data as of 14 September 2018

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



*Male patients; ‡Patient is homozygous for IVS-I-5 β-globin mutation; ^Patient is heterozygous for IVS-I-5 β-globin mutation. Hb, haemoglobin.

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

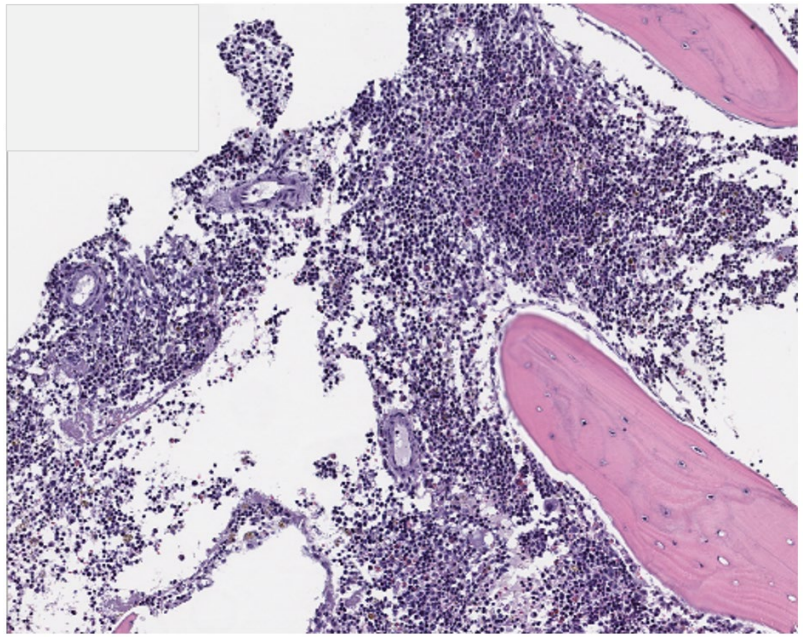


*Last Hb before patient restarted red blood cell transfusions; Hb, haemoglobin

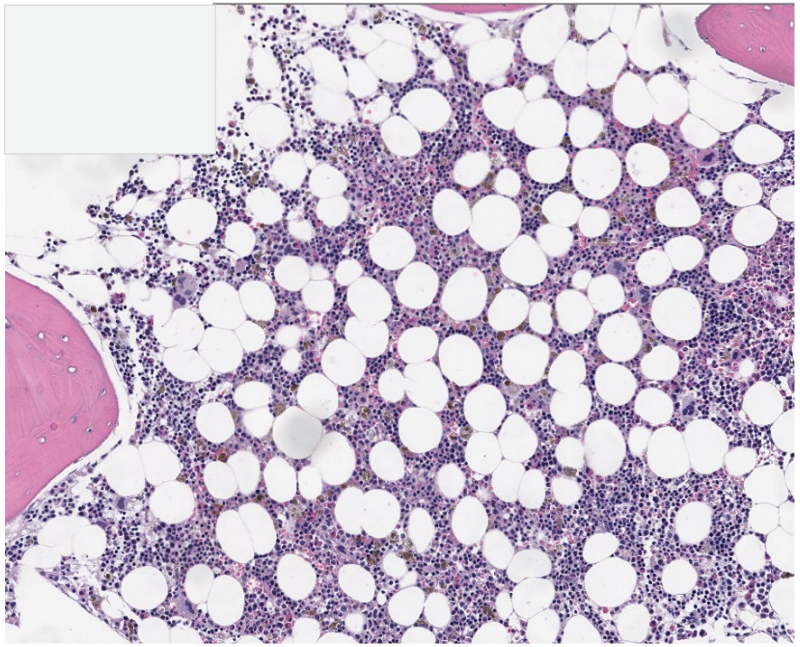
HGB-207: Improvement in erythropoiesis following LentiGlobin gene therapy

Patient 1 (20 yrs old) bone marrow analysis

Screening

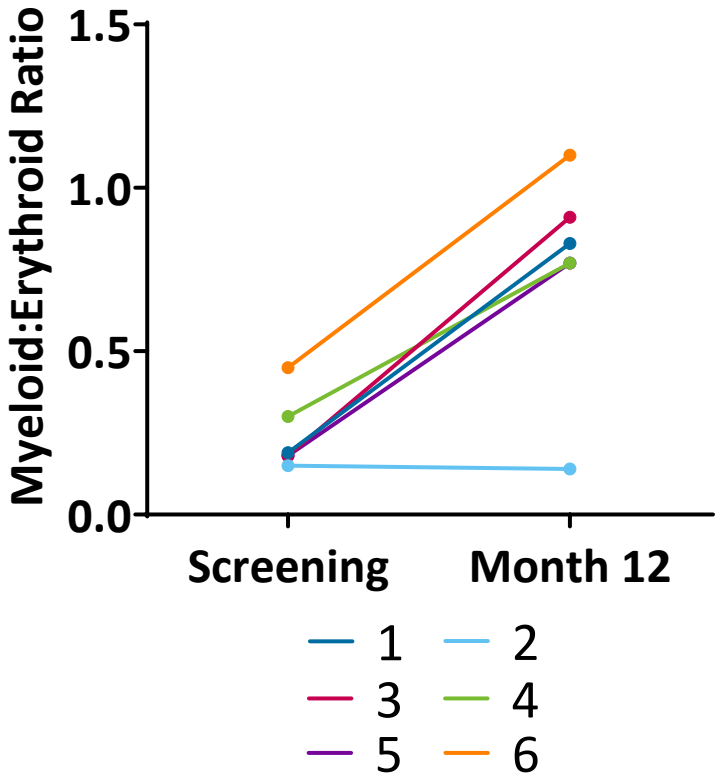


Month 12 post-LentiGlobin



Hb at Month 12: 13.1 g/dL

Myeloid:Erythroid ratio following LentiGlobin gene therapy



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

Hb, haemoglobin

1. Origa R. GeneReviews®. 2018.

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

Non-haematologic* 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

*Haematologic 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-thalassaemia 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

- LentiGlobin manufacturing refinements consistently yield more favorable drug product characteristics
- 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 blood 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
- No deaths, graft-failure, vector-mediated replication-competent lentivirus, or clonal expansion observed to date

AE, adverse event; Hb, haemoglobin

Thank you to the study participants and their families

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