ASH 2018 Abstract #167

Clinical Outcomes of LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassemia Following Completion of the Northstar HGB-204 Study

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Northstar (HGB-204) study of LentiGlobin gene therapy in patients with transfusion-dependent β-thalassemia

- International, multi-center, Phase 1/2, open-label, single-arm study of LentiGlobin gene therapy in adolescents/adults with transfusion-dependent β-thalassemia (TDT)
- Primary objectives: Safety and efficacy of LentiGlobin gene therapy in TDT

All 18 patients have completed the 2-year study

10 patients have ≥ 3 years follow-up

Median follow-up: 38.9 months

(min – max: 29.3 – 48.1 months)

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

TDT, transfusion dependent β-thalassemia

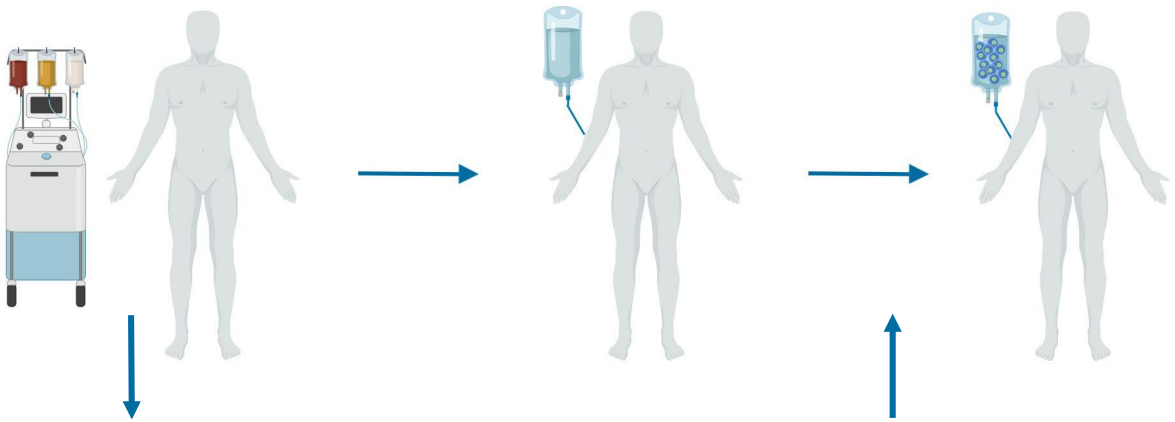
HGB-204: Study design

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

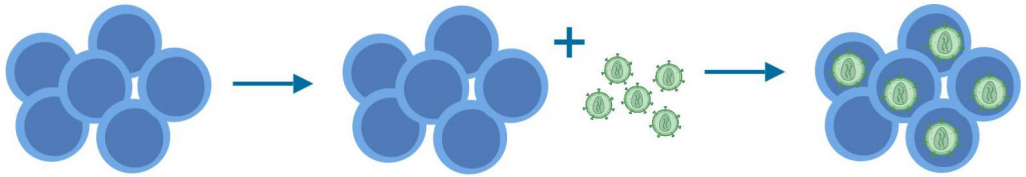
Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs



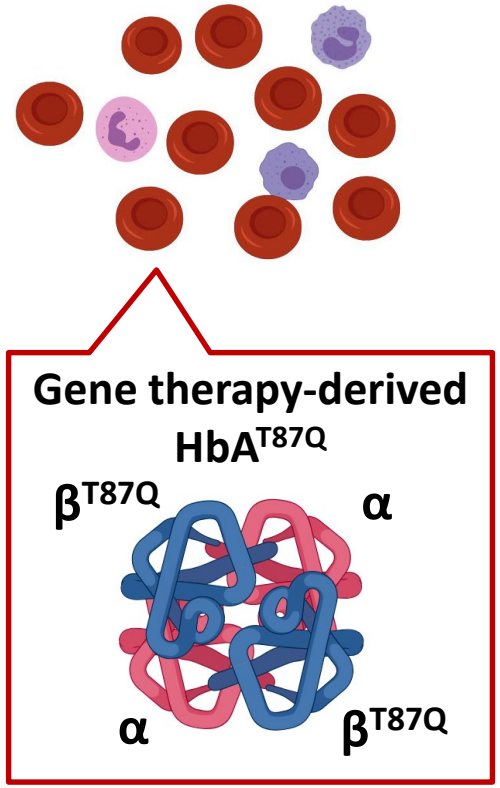
LentiGlobin DP centralized manufacturing



Select CD34+ cells

Transduce with BB305 lentiviral vector

Cryopreserve, test, release DP



2-yr follow-up

Evaluation for Transfusion Independence*

Long-Term Follow-Up Study

*Transfusion Independence is defined in the protocol as weighted average hemoglobin ≥9 g/dL without any transfusions for ≥12 months
DP, drug product; 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), years		**20** (12 – 35)
Pre-study pRBC transfusion volume annualized median (min – max), mL/kg/yr		**169** (124 – 273)
Liver iron concentration median (min – max), mg Fe/g dw		**5.7** (0.4 – 26.4)

Drug Product Characteristics	N = 18 median (min – max)
Drug product cell dose CD34+ cells x10^6/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[#] study day	**18.5** (14 – 30)
Platelet engraftment[^] study day	**39.5** (19 – 191)

†22 drug product lots manufactured for 18 patients; #Absolute neutrophil count ≥ 500 cells/µL for 3 consecutive days; ^Unsupported platelet count ≥ 20,000 platelets/µL.
pRBC, packed red blood cells; VCN, vector copy number

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

Non-hematologic* grade ≥ 3† AEs reported in ≥2 patients *DP 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 *DP infusion to last follow-up*	
Thrombosis§	2 (11)
Veno-occlusive liver disease‡	2 (11)

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

- No grade ≥ 3 DP-related AEs
- No deaths or graft failure
- No vector-mediated replication competent lentivirus
  - HIV infection serious AE was reported 23 months after DP infusion
    - Wild-type HIV-1 was documented
    - Not related to BB305 vector in LentiGlobin

AE, adverse event; DP, drug product; HIV, human immunodeficiency virus

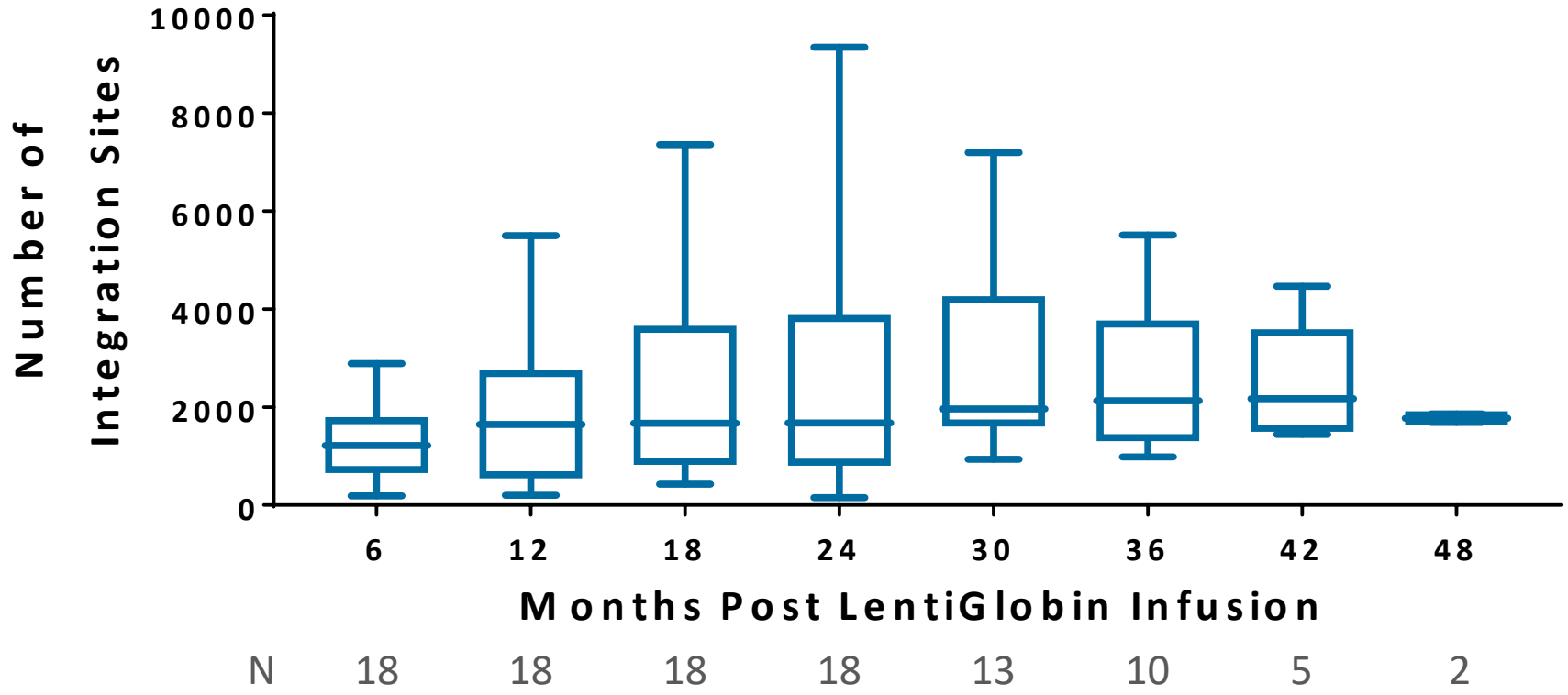
HGB-204: Integration site analysis shows polyclonal vector integration profile is maintained over time

(nr)LAM-PCR was used to evaluate the LentiGlobin BB305 lentiviral vector integration profile

No clonal dominance has been observed

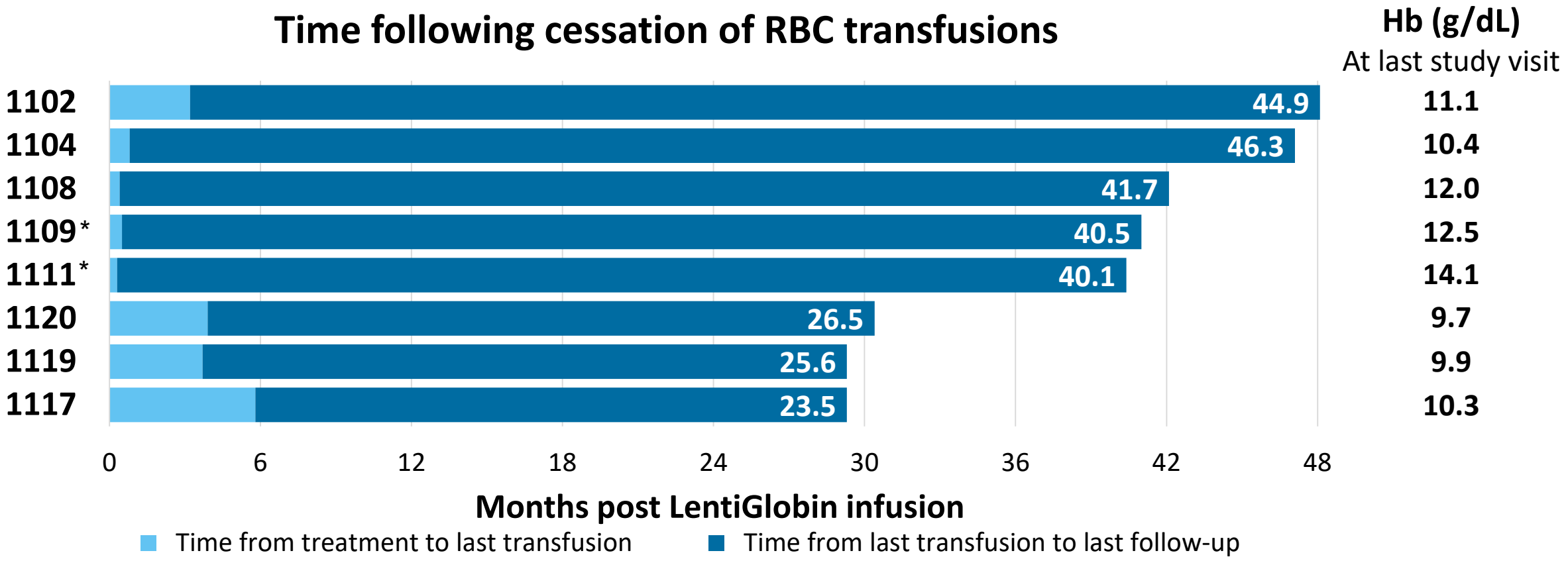
No single integration site contributed to more than 30% of all integration sites at any time

3 integration sites in 2 patients contributed to 20 – ≤ 30% integration sites at any time



(nr)LAM-PCR, non-restrictive linear amplification-mediated polymerase chain reaction

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

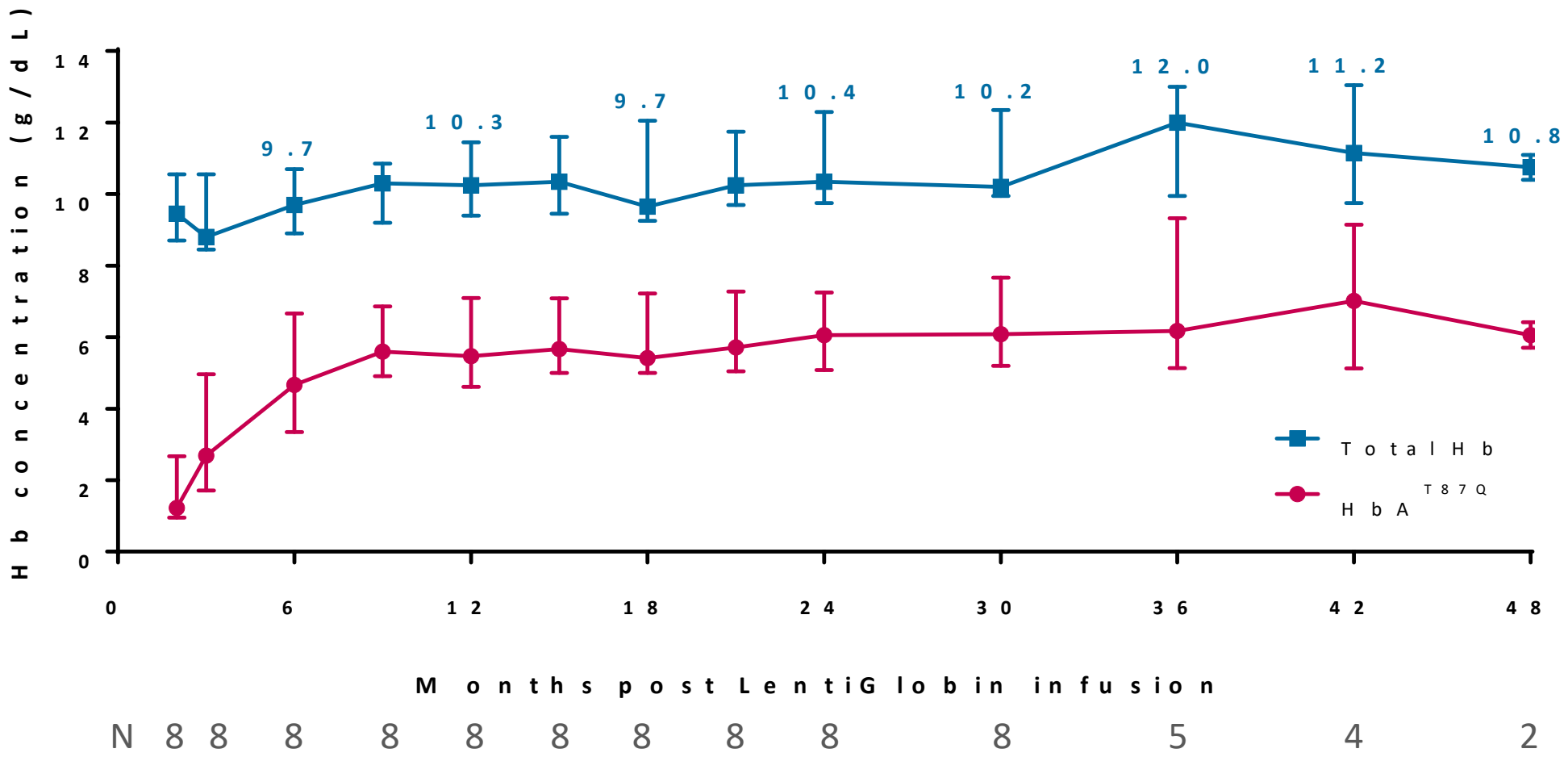


Median duration of TI: 38.0 months (min – max: 21.2 – 43.6 months); responses are ongoing
Median weighted average Hb during TI: 10.2 g/dL (min – max: 9.3 – 13.2 g/dL)

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

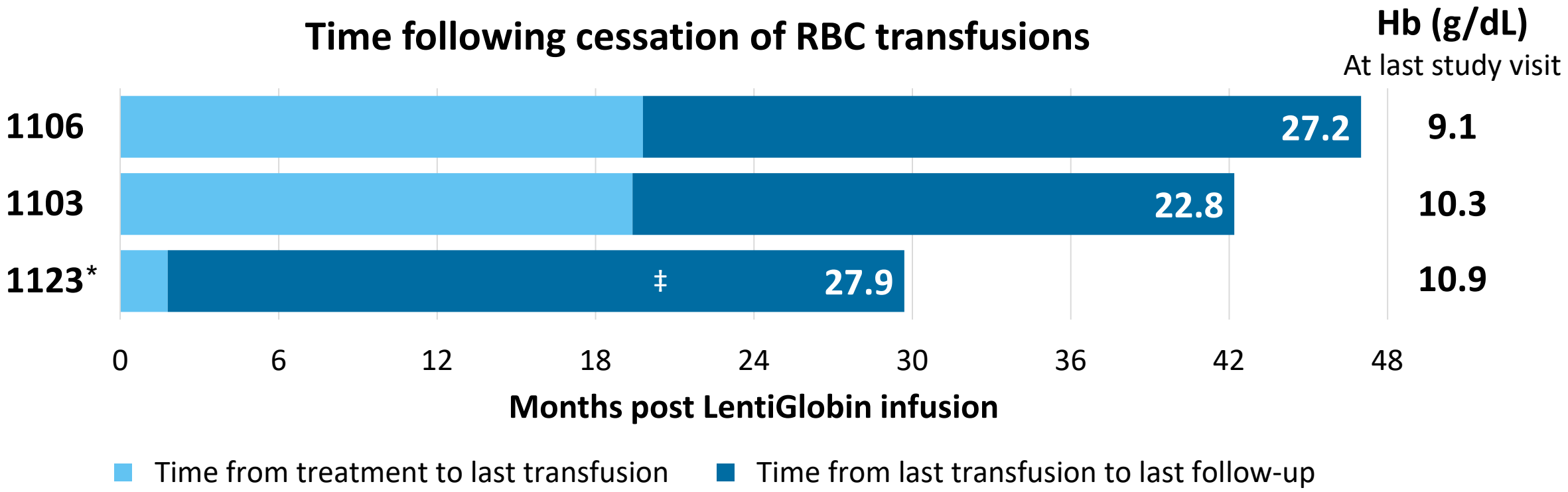
HGB-204: HbA^{T87Q} expression in blood is stable post-LentiGlobin

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



Medians (Q1, Q3) depicted; Hb, hemoglobin

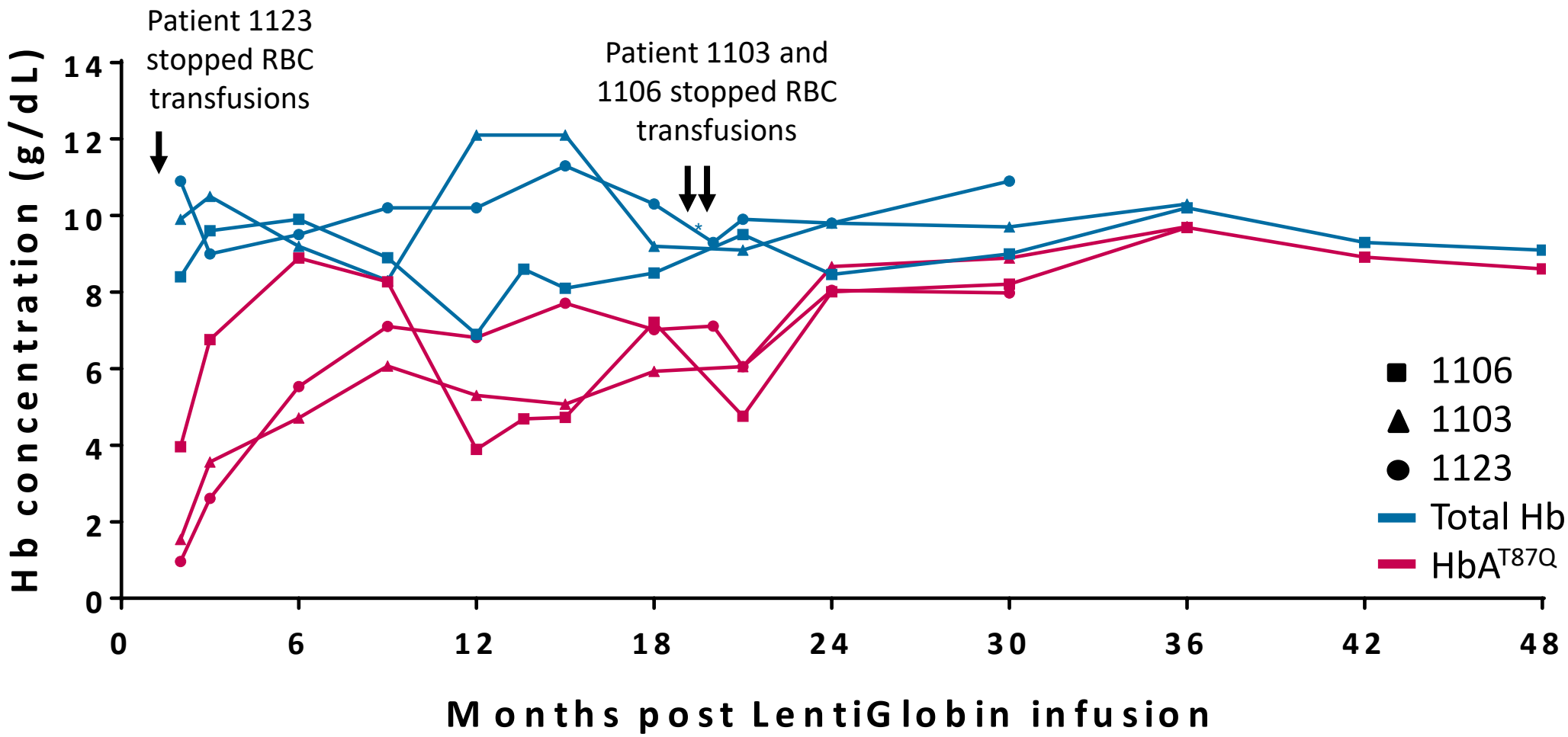
HGB-204: 3/8 patients with β^0/β^0 genotypes have achieved transfusion independence



Median duration of TI: 16.4 months (min – max: 16.1 – 20.8 months)
Median weighted average Hb during TI: 9.9 g/dL (min – max: 9.5 – 10.1 g/dL)

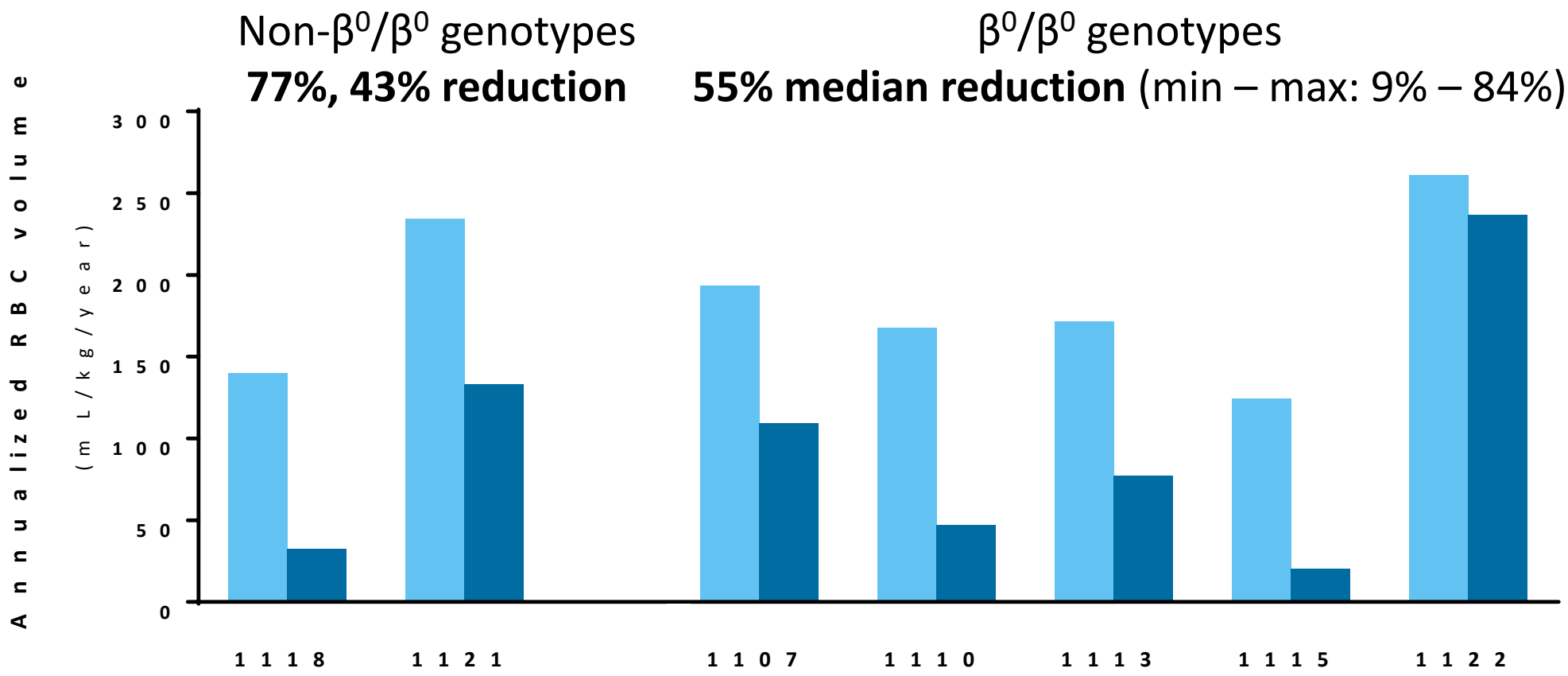
*Indicates male patient
‡Patient had a single transfusion for an acute event of cat scratch disease
Hb, hemoglobin; TI, transfusion independence (weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months)

HGB-204: Hb in patients with β^0/β^0 genotypes who achieved transfusion independence



*Patient 1123 had a single transfusion for an acute event of cat scratch disease

HGB-204: Reduction in RBC transfusion volume in patients still receiving transfusions



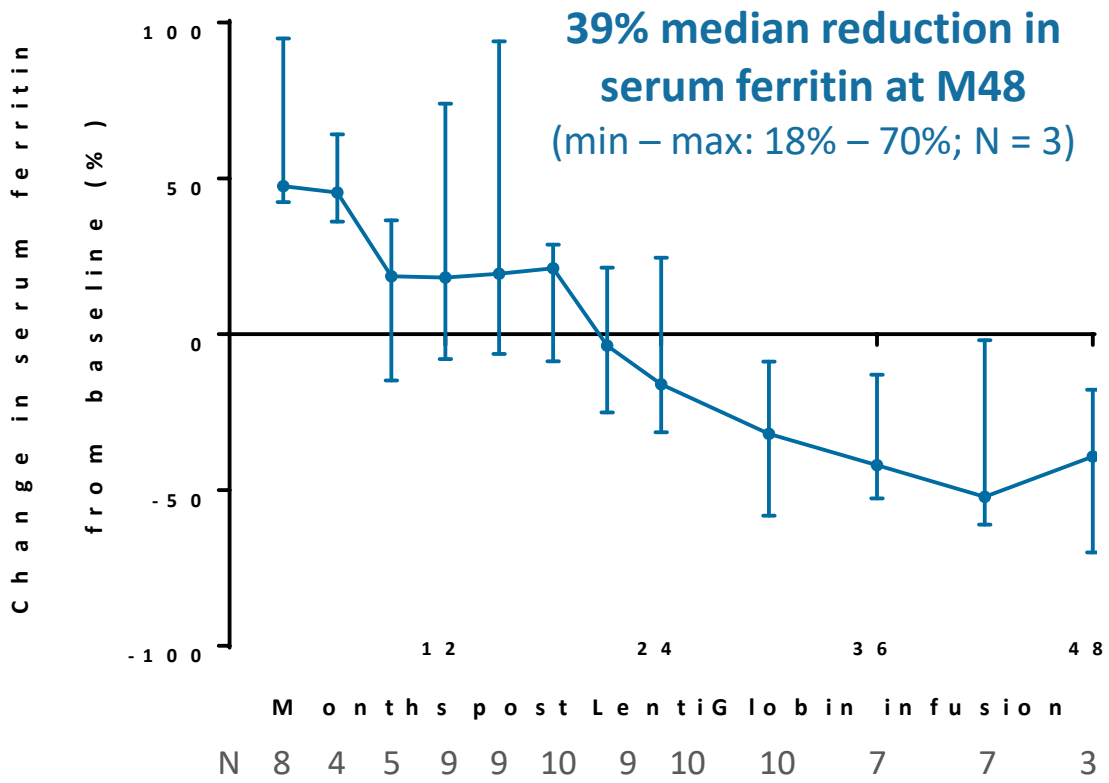
Pre-treatment: Annualized volume of RBC transfusions in the 2 years prior to study enrollment

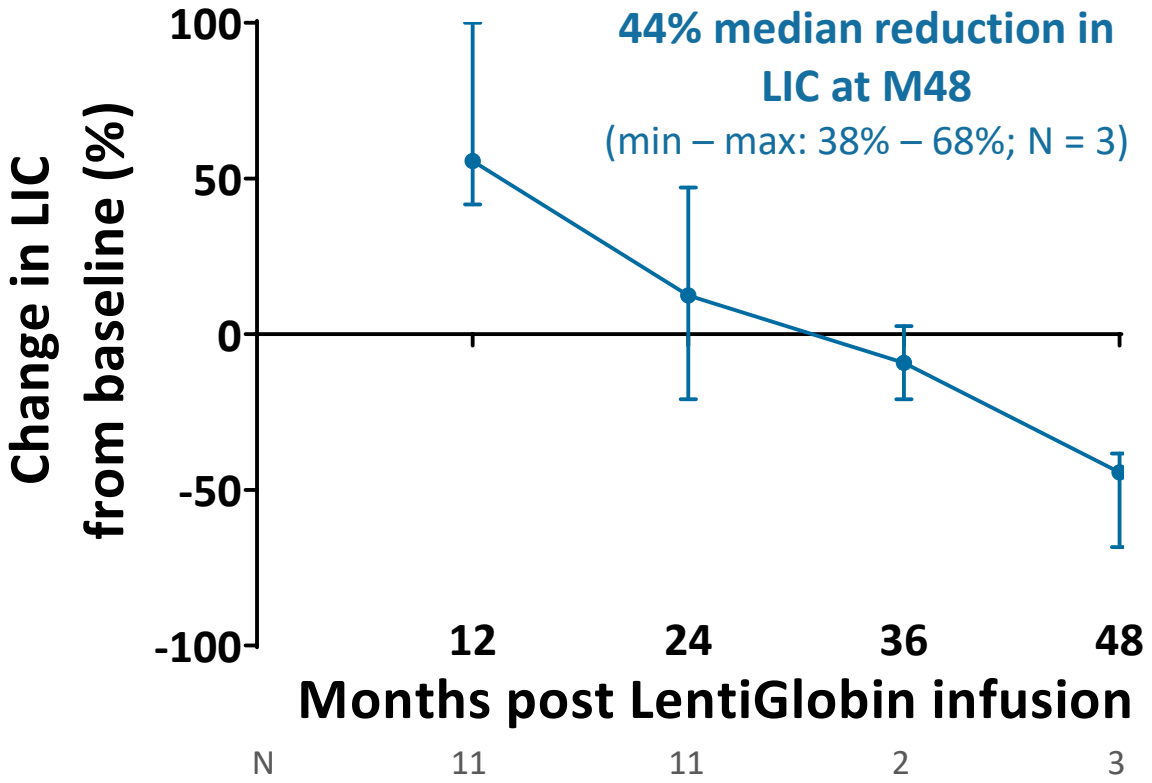
Post-treatment: Annualized on-study volume of RBC transfusions starting at month 6 post-DP infusion through last study visit

RBC, red blood cell

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

% Change in serum ferritin and LIC from baseline in patients 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. One patient did not have a baseline serum ferritin level. LIC, liver iron concentration; TI, transfusion independence

Phase 3 clinical studies of LentiGlobin in transfusion-dependent β-thalassemia

HGB-207

Phase 3, multi-center, global study
NCT02906202

- Non-β^0/β^0 genotypes
- N = 23 patients ≤ 50 years of age
- Ongoing

HGB-212

Phase 3, multi-center, global study
NCT03207009

- β^0/β^0 genotypes*
- N = ~15 patients ≤ 50 years of age
- Ongoing

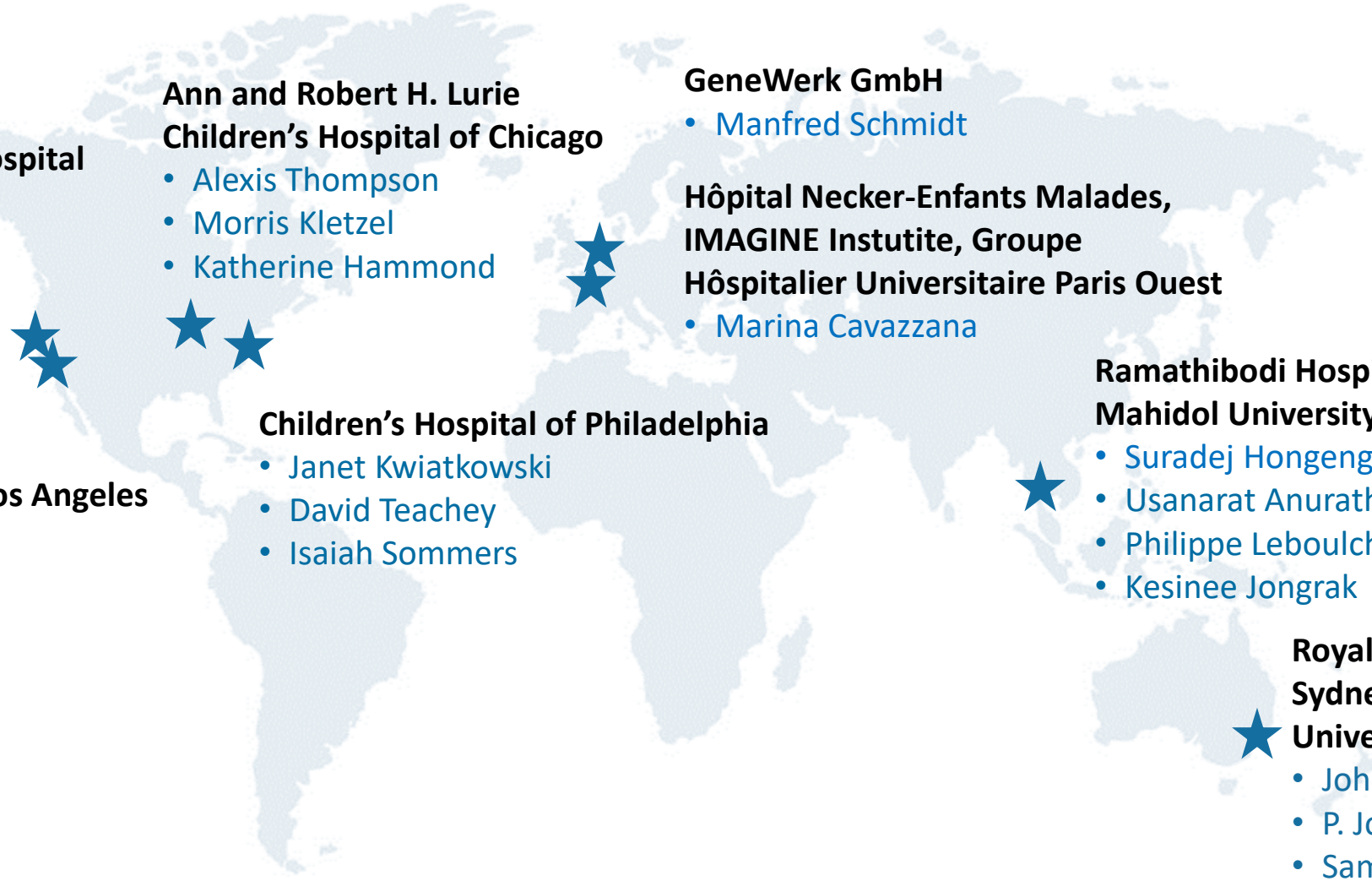
*Includes patients with the β^+ *HBB* mutation IVS I-110 (G→A)

HGB-204 (Northstar) Study: Summary

- 80% (8/10) patients with non-β^0/β^0 genotype and transfusion dependent β-thalassemia have achieved durable transfusion independence with up to 4 years follow-up
  - Median duration of transfusion independence of 38 months
  - Hb levels were 9.7 – 14.1 g/dL at last study visit and HbA^{T87Q} remains stable
  - 2/10 patients without transfusion independence had transfusion volume reduced by 77% and 43%
- 38% (3/8) patients with β^0/β^0 genotypes have achieved transfusion independence
  - Transfusion volume was reduced by a median of 55% in 5/8 patients
- Reduced iron burden observed in patients achieving transfusion independence
- The safety profile of LentiGlobin is consistent with myeloablative conditioning
  - Some patients had delayed platelet engraftment after DP infusion

Hb, hemoglobin; TI, transfusion independence

Thank you to the study participants and their families



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