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Safety and Efficacy of LentiGlobin Gene Therapy for Transfusion-Dependent β-thalassemia (TDT) in Patients with non-β^0/β^0 Genotypes: Interim Results from the HGB-204 (Northstar) and HGB-207 (Northstar-2) Trials

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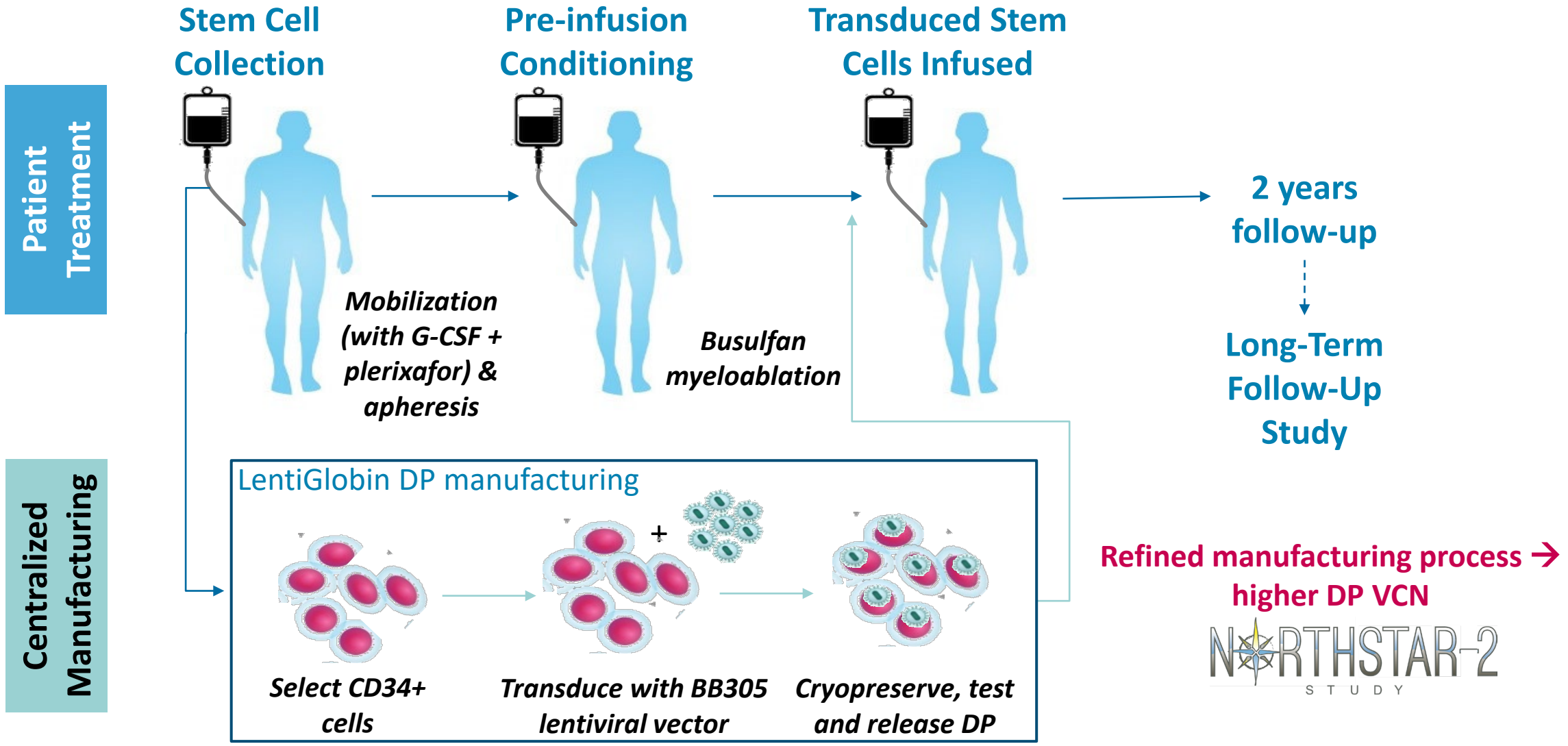
HGB-204 (Northstar) and HGB-207 (Northstar-2) study designs



HGB-204 (Northstar) study of LentiGlobin BB305 gene therapy in TDT

- International, multi-center, Phase 1/2, open-label, single-arm study in adolescents/adults with TDT
- Primary objectives: Safety and efficacy of LentiGlobin Drug Product in TDT
- **18 treated patients** (fully enrolled)
  - β^0/β^0 genotypes (n=8); Non-β^0/β^0 genotypes (n=10)
  - Ages: 18 – 35y (n=15), 12 – 17y (n=3)
- Median follow-up for all patients: **27.4 months** (min – max: 17.5 – 36.5 months)

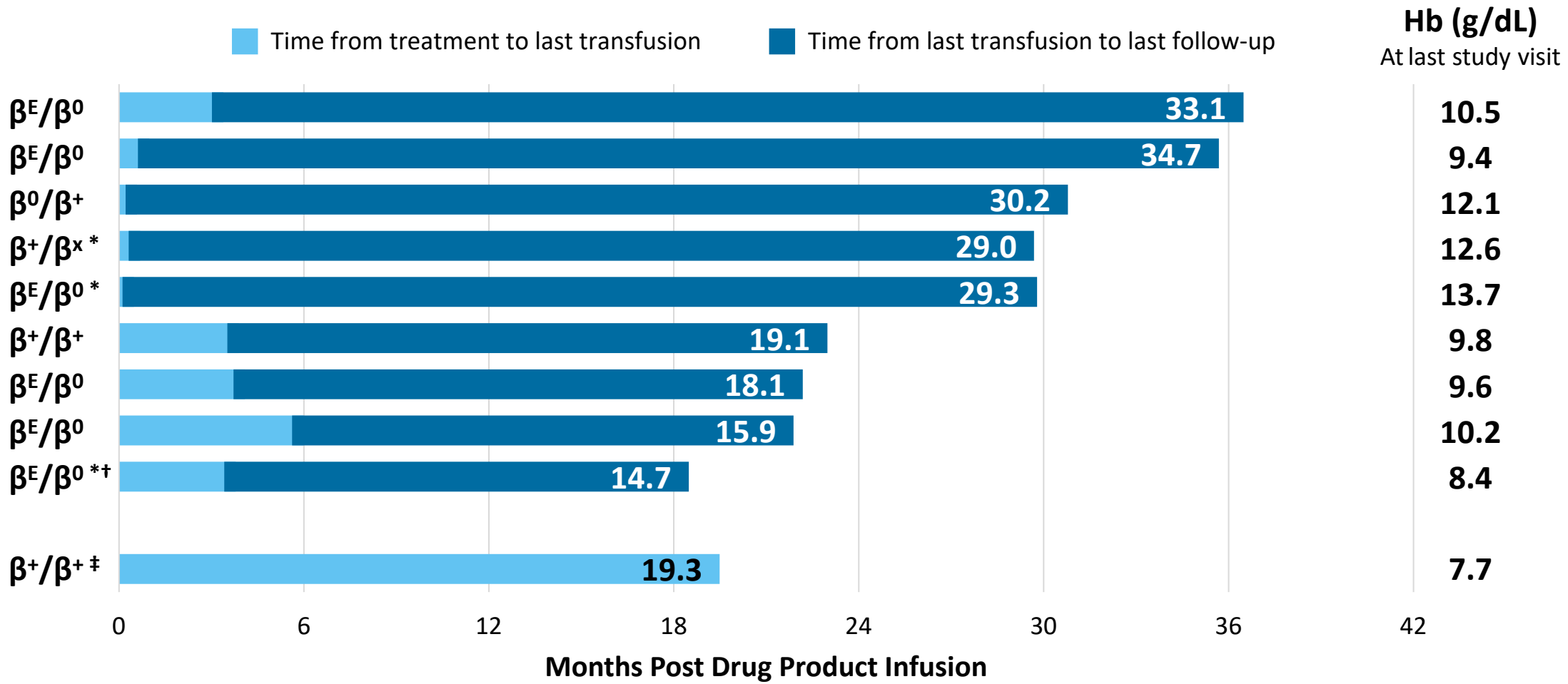
- **All 18 patients have ≥ 18 months follow-up**
- **10 patients have completed 2-year analysis**
- **3 patients have 3 years follow-up**

TDT, transfusion dependent β-thalassemia

9/10 patients with non-β^0/β^0 genotypes are free from chronic RBC transfusions

HGB-204

Median of 29 months free from chronic transfusions in 9/10 patients



*Indicates male patients; †Patient received a single transfusion at Month 13 during an acute illness; ‡DP VCN of 0.3

HGB-207 (Northstar-2): Study disposition

International, multi-center, Phase 3, open-label, single-arm study in adolescents/adults with TDT and a non-β^0/β^0 genotype

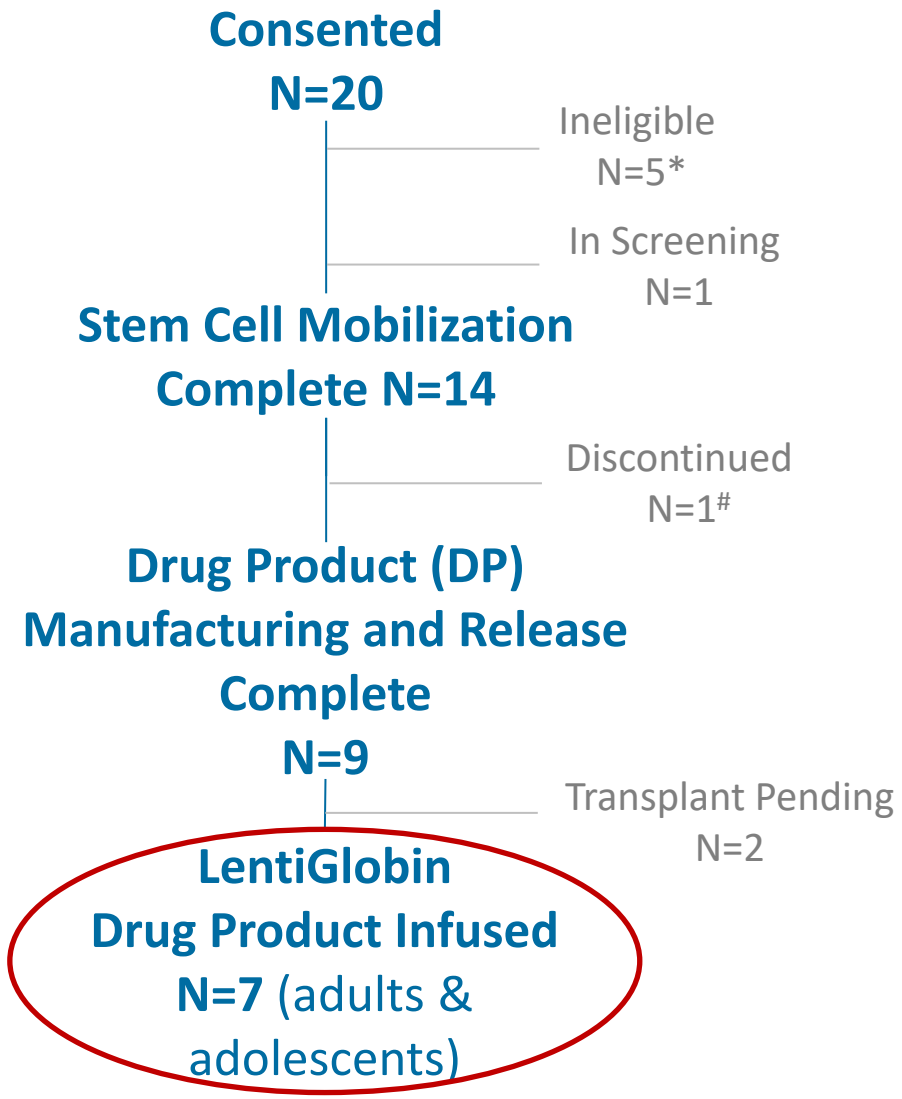
Key enrollment criteria

- 12 to 50 years of age
- Non-β^0/β^0 genotypes
- RBC requirement: ≥100 ml/kg/year (or ≥8 pRBC transfusions/yr) for past 2 years
- Adequate organ function/performance status
- No previous HSCT or gene therapy
- **Target: LentiGlobin DP infused in 15 patients**

Primary endpoint:

% patients who achieve **transfusion independence**

i.e., maintain weighted average Hb ≥9 g/dL without RBC transfusions for ≥12 months



*Reasons for ineligibility: 2 withdrew consent, 3 screen failure due to advanced liver disease
#Subject discontinued because of positive pregnancy test prior to undergoing conditioning

Patient and treatment characteristics

Patient Characteristics

		HGB-207 (N = 7)	HGB-204 (N = 10)
Genotypes	β^E/β^0	**3**	**6**
	Other	**4** (2 β^+/β^+, 2 β^+/β^0)	**4** (2 β^+/β^+, 1 β^+/β^0, 1 β^+/β^x)
Gender		**4 Female**	**7 Female**
Age at consent median (min–max), years		**20** (15 – 24)	**20** (16 – 34)
Pre-study pRBC transfusion volume annualized median (min–max), mL/kg/yr		**192.9** (158.7 – 240.5)	**146.9** (139.1 – 234.5)
Liver iron concentration median (min–max), mg/g		**7.2** (1.4 – 19.6)	**5.7** (1.2 – 26.4)
Cardiac T2* median (min–max), msec		**36.4** (35.3 – 45.3)	**37.5** (27.0 – 54.0)
Splenectomy n, %		**2** (29)	**3** (30)

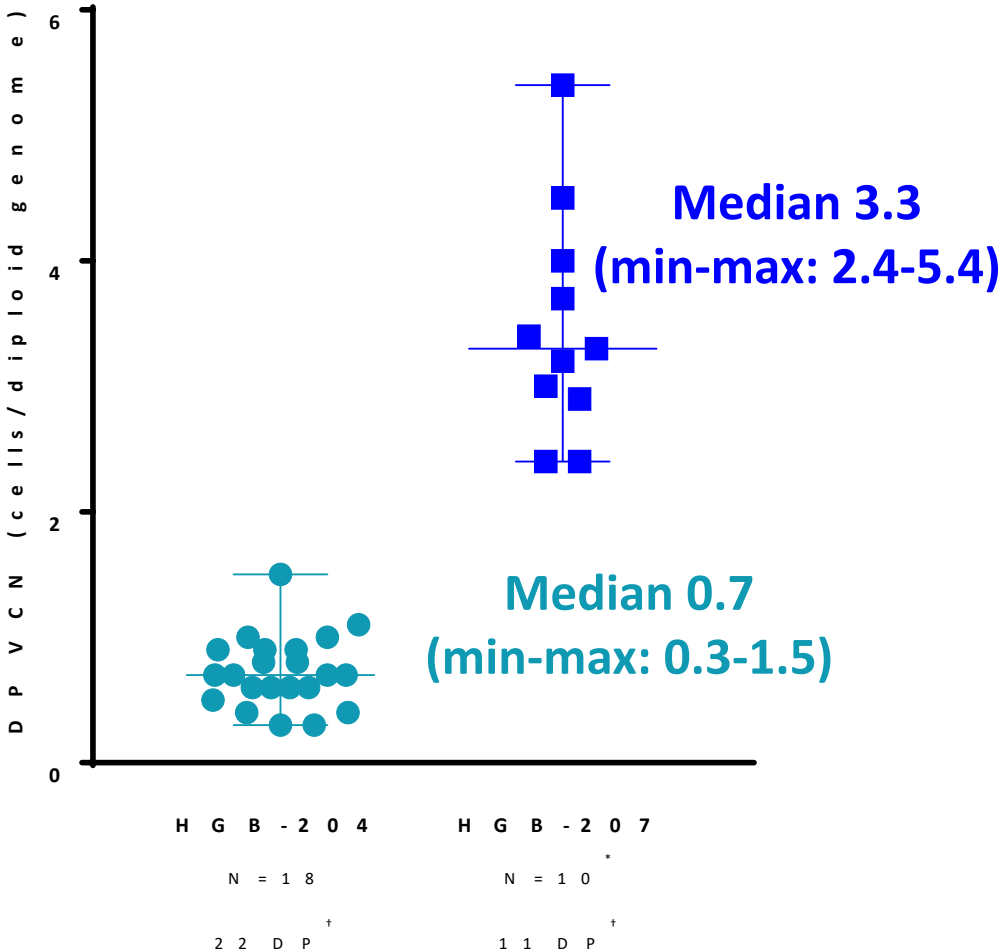
Treatment Characteristics

	HGB-207 (N = 7)	HGB-204 (N = 10)
Drug product cell dose median (min–max), CD34+ cells x10^6/kg	**7.9** (5.2 – 13.6)	**7.1** (5.2 – 13.0)
Busulfan AUC[†] median (min–max), µM*min	**4562** (4205 – 4988)	**4060** (3030 – 4416)
Neutrophil engraftment[‡] median (min–max), study day	**21.5**[#] (17 – 26)	**18.5** (14 – 27)
Platelet engraftment[¶] median (min–max), study day	**44**[#] (35 – 46)	**50.5** (19 – 191)
Follow-up median (min-max), month	**3** (1 – 9)	**26.1** (18.2 – 36.3)

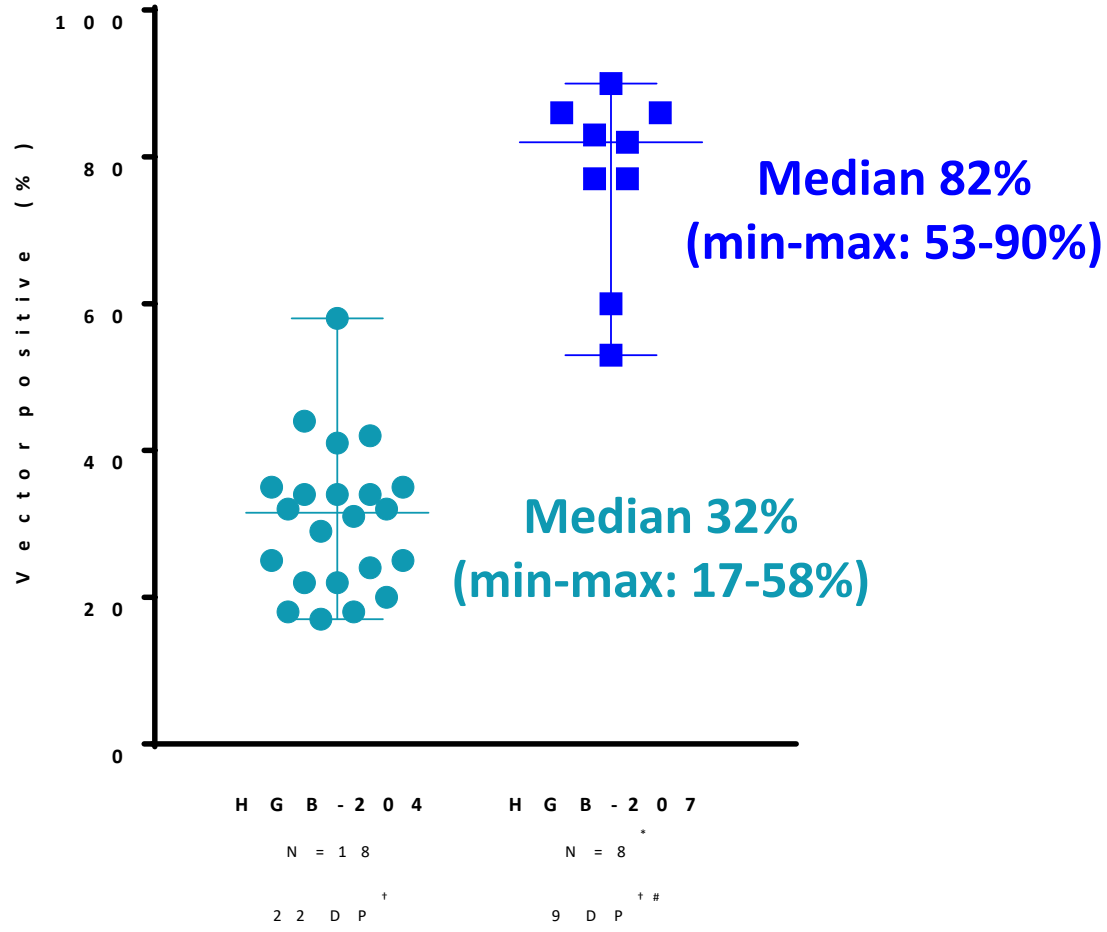
[†]Estimated average daily busulfan exposure over 4 days; [‡]ANC ≥500 cells/µL for 3 consecutive days; [#]N=6; 1 patient with < 1 month follow-up had not engrafted as of data-cut off date;
[¶]Unsupported platelet count ≥ 20,000/µL; ANC, absolute neutrophil count; AUC, area under the curve; DP, drug product; pRBC, packed red blood cells; TDT, transfusion-dependent β-thalassemia.

Refined manufacturing process yielded improved drug product characteristics

Vector copy number (VCN) in drug product



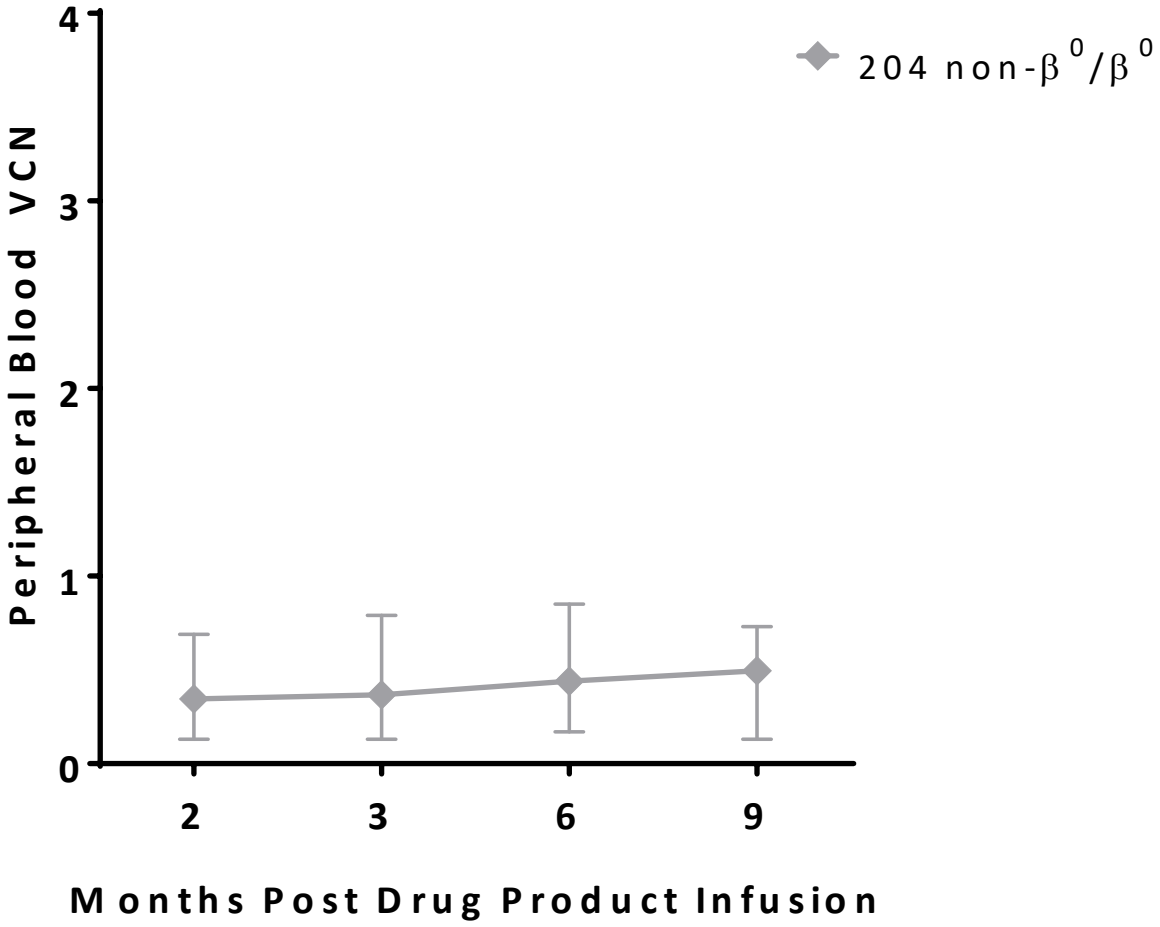
Proportion of CD34+ cells transduced



*As of Oct 13, 2017 in the 7 treated patients, the median DP VCN was 3.1 (min – max 2.4 – 4.0) and the median % CD34+ cells transduced was 77% (min – max 53 – 90);
†No of DP exceed number of patients since some patients were mobilized twice; #LVV not available for 2 DP at time of analyses

Higher PB VCN and HbA^{T87Q} in HGB-207 vs HGB-204

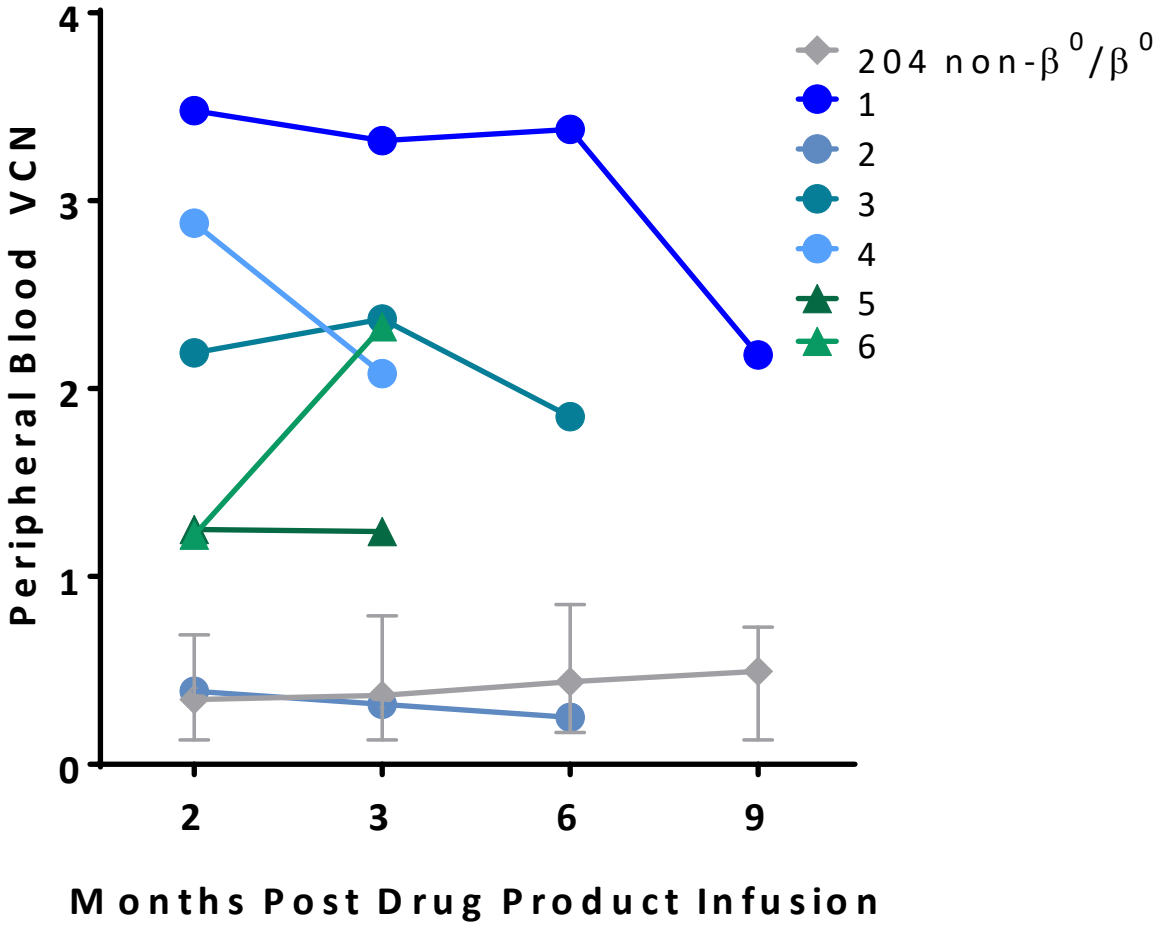
Peripheral blood VCN



For 204 non-β^0/β^0 pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

Higher PB VCN and HbA^{T87Q} in HGB-207 vs HGB-204

Peripheral blood VCN



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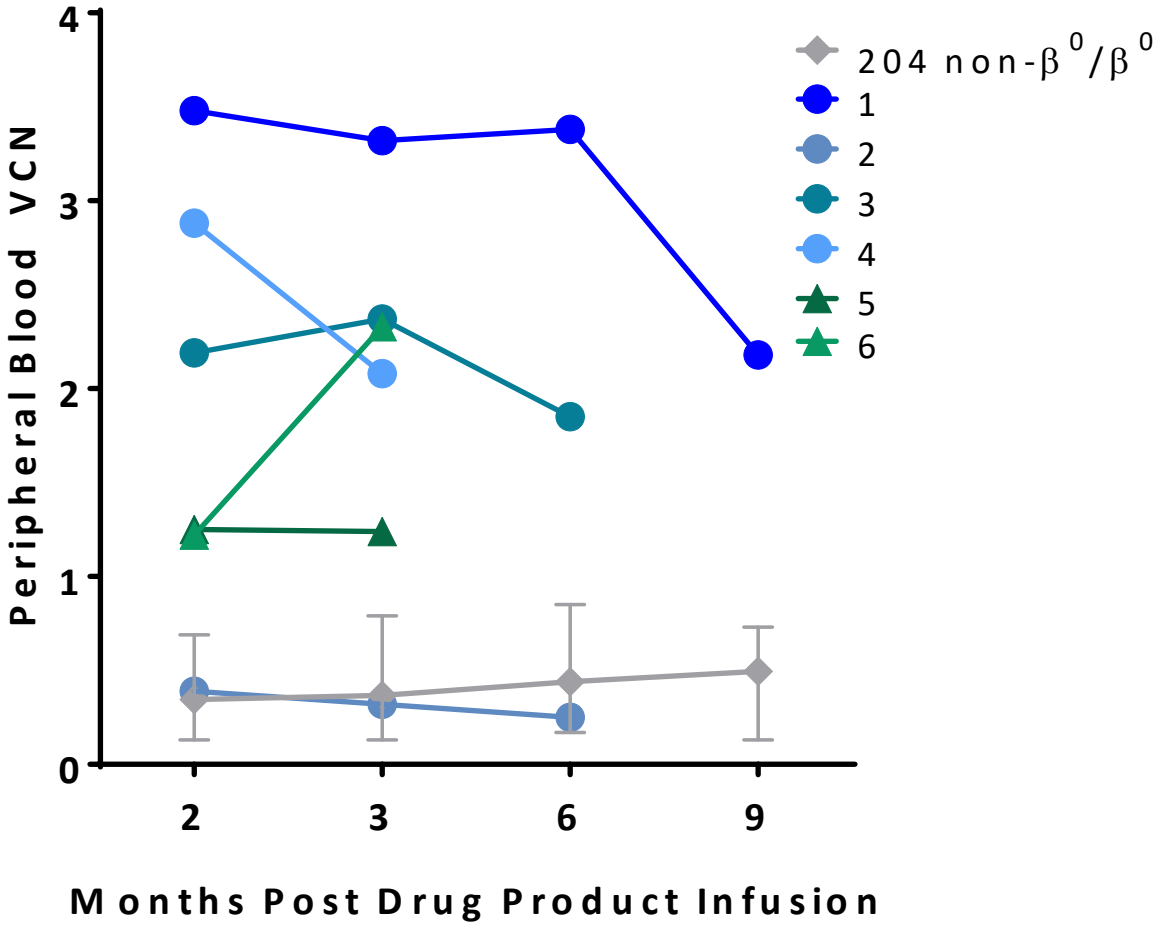
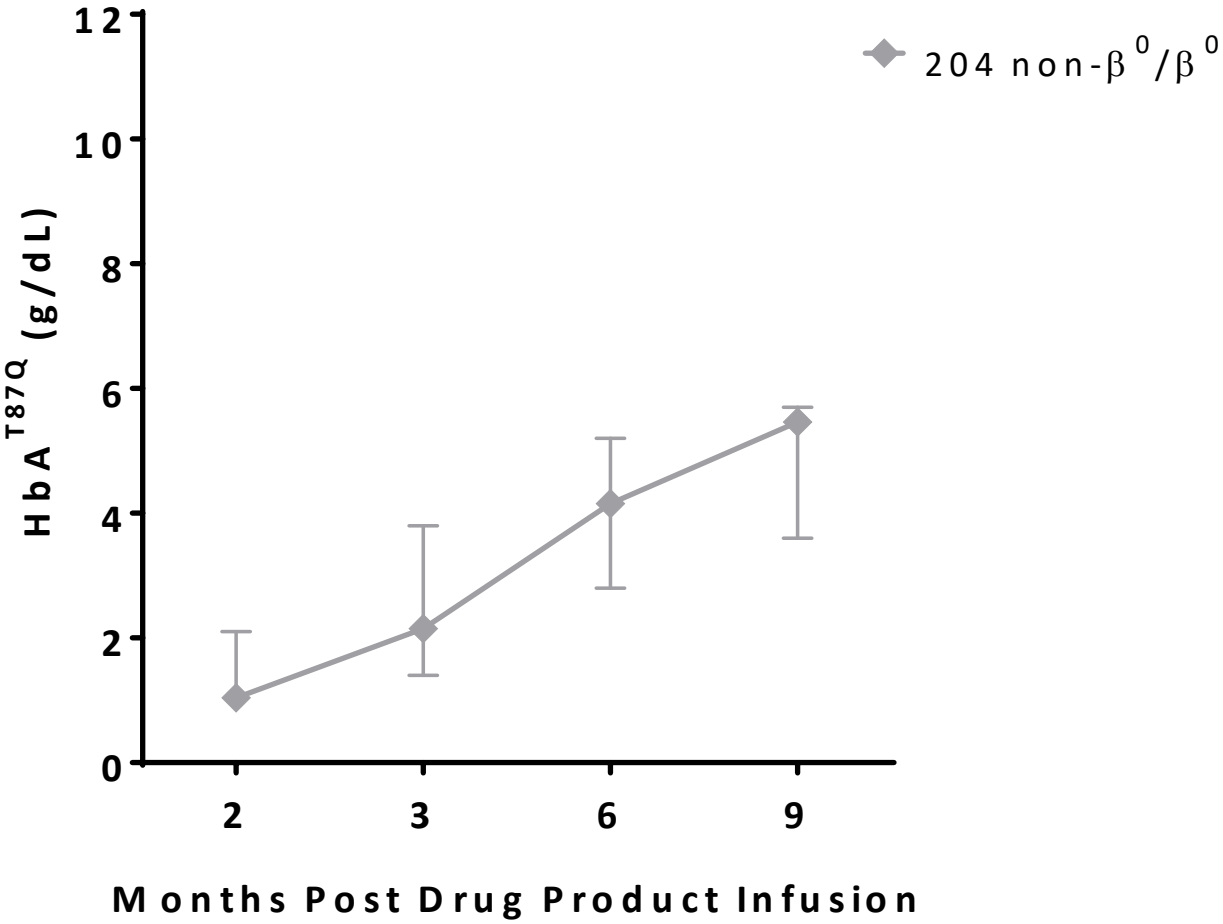
Peripheral blood VCN



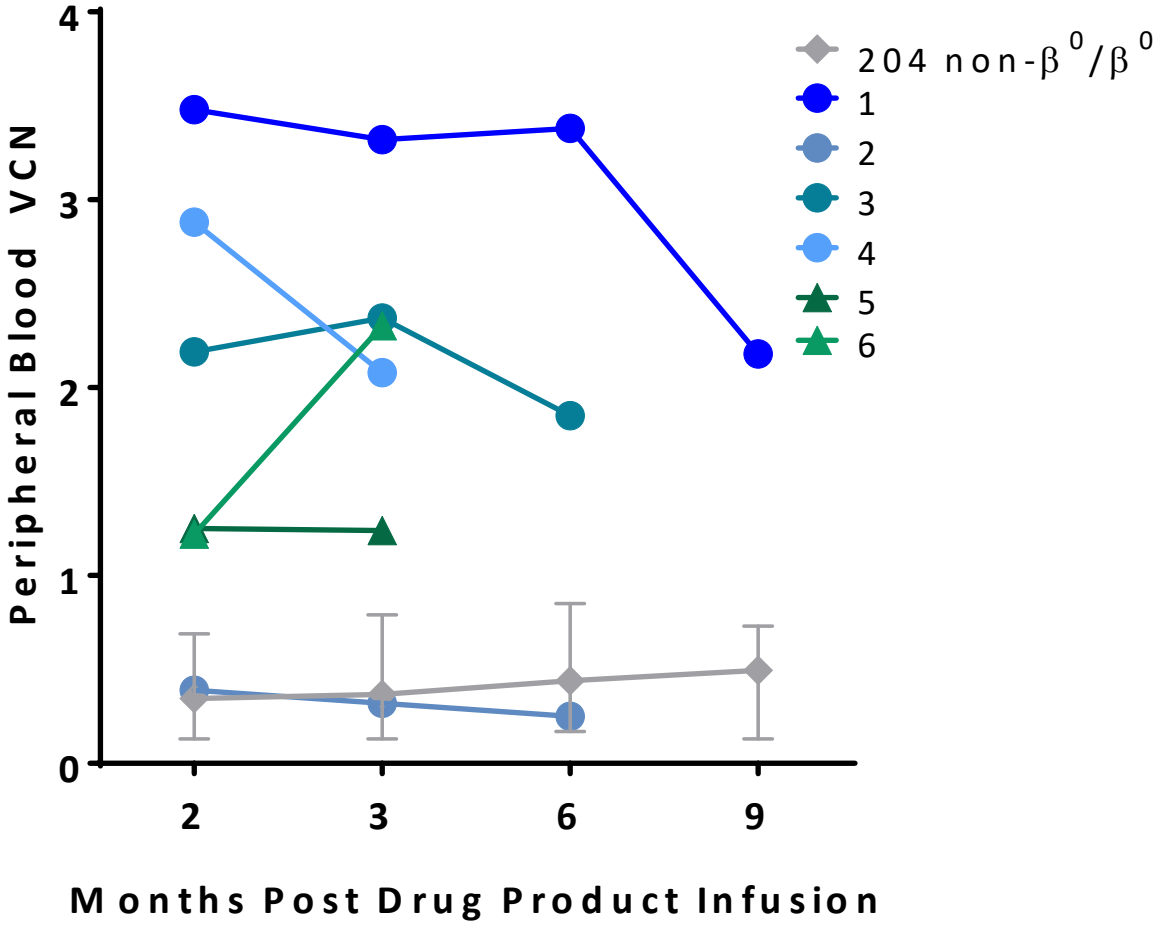
HbA^{T87Q}



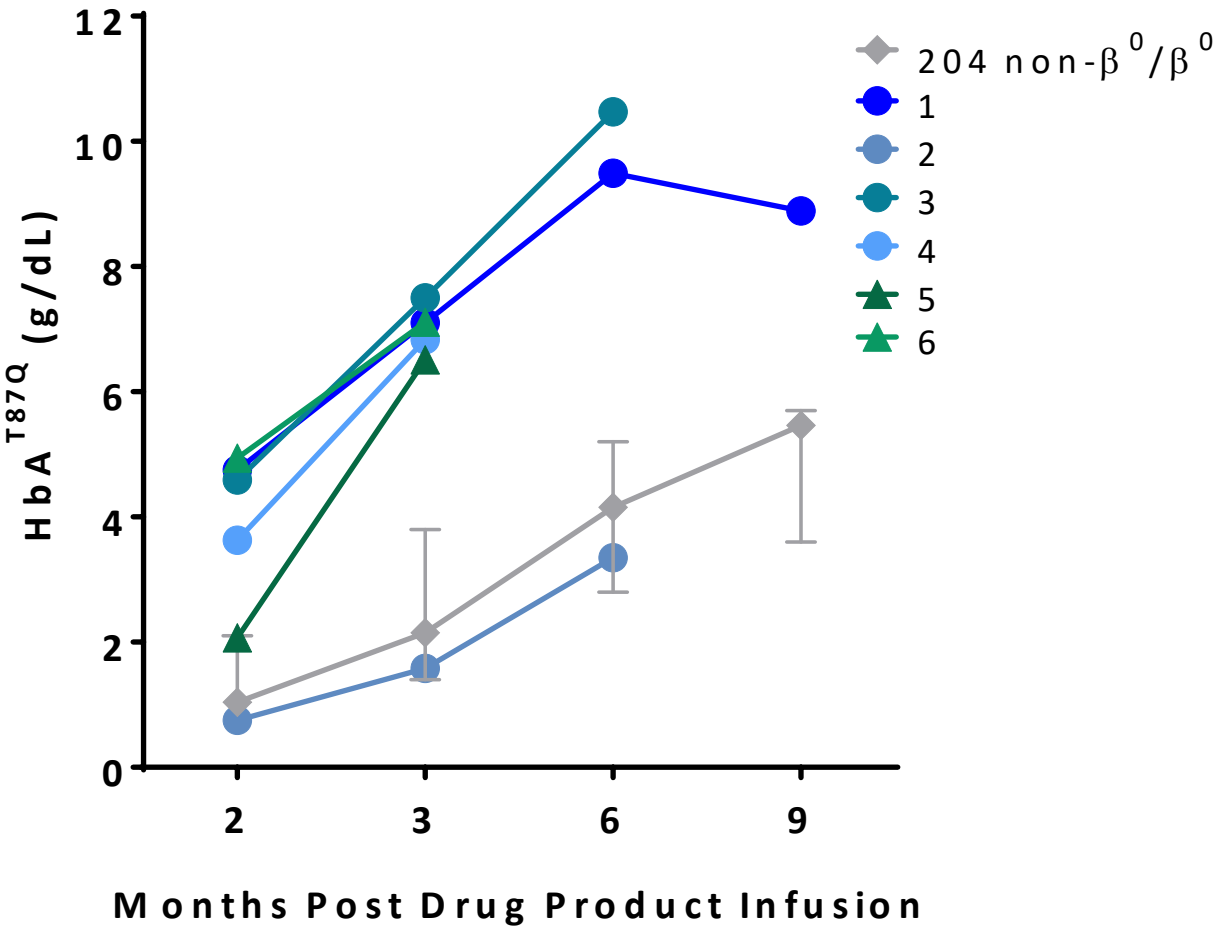
For 204 non-β^0/β^0 pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

Higher PB VCN and HbA^{T87Q} in HGB-207 vs HGB-204

Peripheral blood VCN



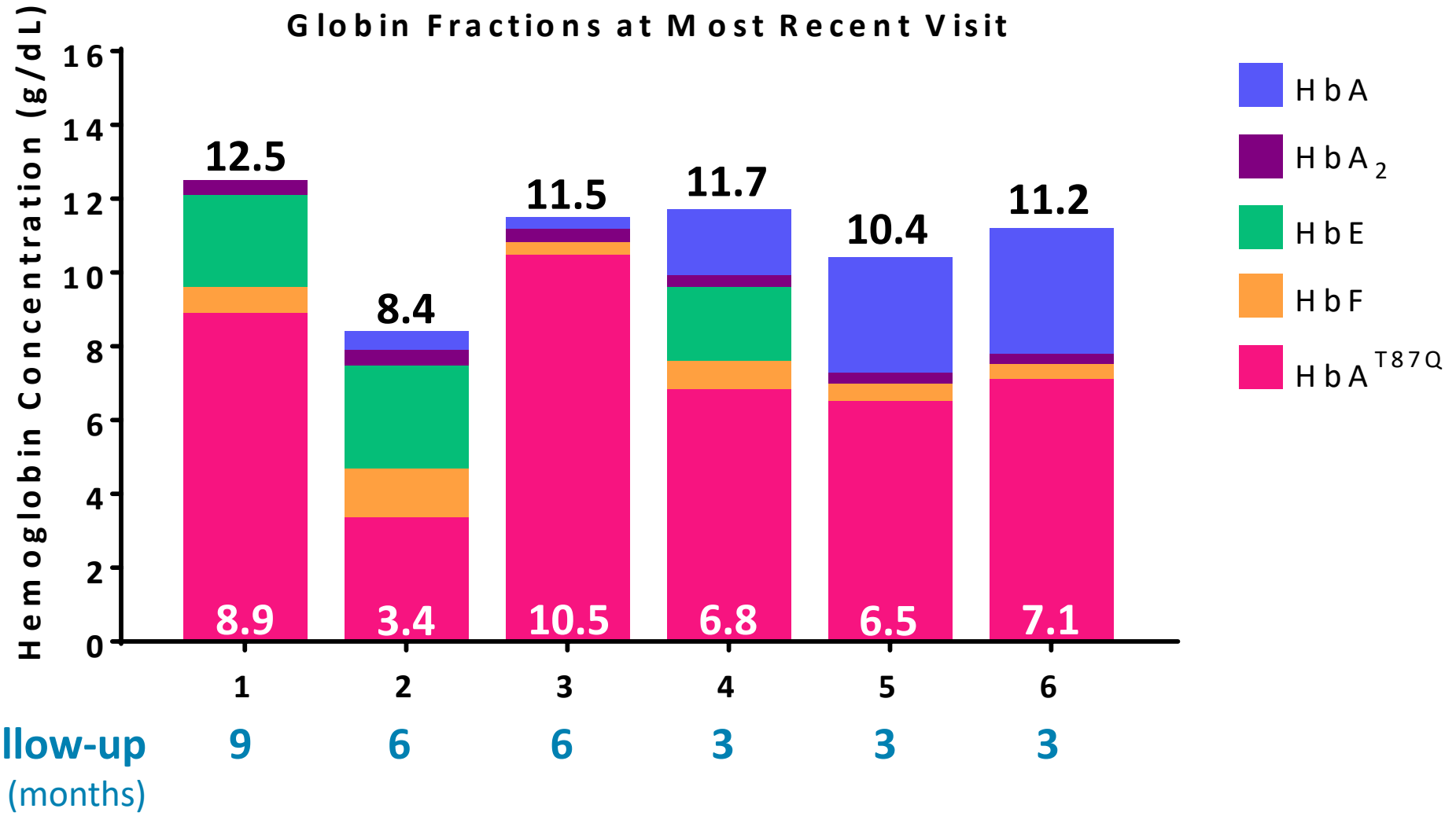
HbA^{T87Q}



For 204 non-β^0/β^0 pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

5 of 6 patients making at least 6 g/dL of HbA^{T87Q} at ≥3 months

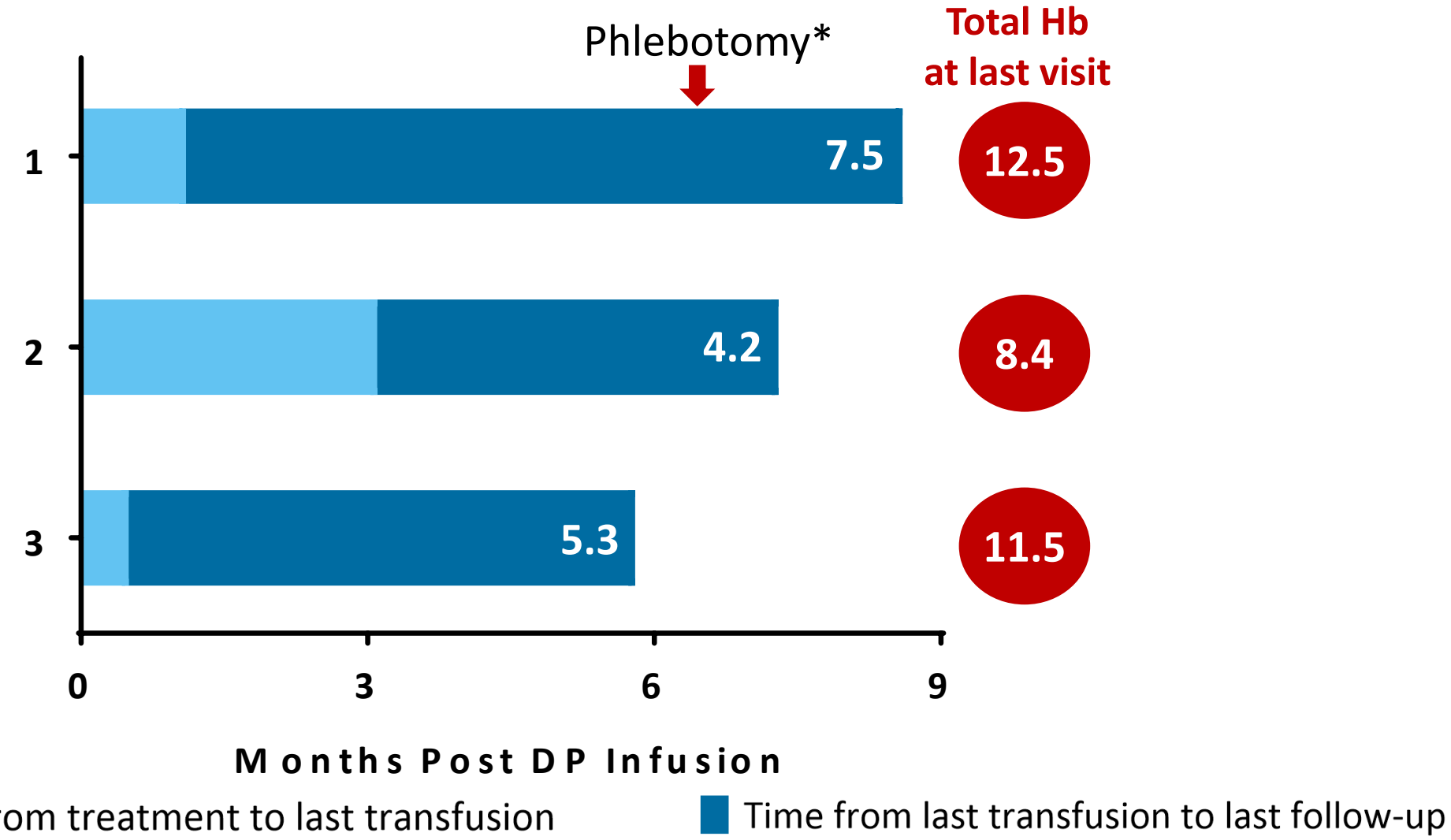
HGB-207



Median (Q1, Q3) HbA^{T87Q} at 3 and 9 months in Northstar (HGB-204) was 2.2 (1.4, 3.8) and 5.5 (3.6, 5.7), respectively

Patients with ≥ 6 months follow-up have 4 – 7 months without RBC transfusion

HGB-207



*Started 6 months post DP infusion

Safety profile is generally consistent with myeloablative conditioning

HGB-204 (N=10*)

Non-hematologic† grade ≥3 AEs in ≥2 patients *DP infusion to up to 2 years of follow-up*	Patient Incidence n (%)
Stomatitis	8 (80)
Febrile neutropenia	6 (60)
Irregular menstruation	2 (20)
Pharyngeal inflammation	2 (20)
Serious AEs *DP infusion to last follow-up*	
Acute gastroenteritis	1 (10)
Appendicitis	1 (10)
Central venous catheter thrombosis	1 (10)
Infectious diarrhea	1 (10)
Veno-occlusive liver disease	1 (10)

HGB-207 (N=7)

Non-hematologic† grade ≥3 AEs in ≥2 patients *DP infusion to last follow-up*	Patient Incidence n (%)
Stomatitis	3 (43)
ALT increase	2 (29)
Serious AEs *DP infusion to last follow-up*	
Transfusion reaction	1 (14)
Hypotension	1 (14)

- **No grade ≥ 3 DP-related AEs**
- **No graft failure and no deaths**
- **No replication competent lentivirus**
- **No evidence of clonal dominance**

*AEs are presented for patients with TDT and non-β^0/β^0 genotypes; †Hematologic AEs commonly observed post-transplant have been excluded.
AEs, adverse evets; ALT, alanine aminotransferase; DP, drug product; TDT, transfusion-dependent β-thalassemia

Summary

- In HGB-204, 9/10 patients with TDT and non-β^0/β^0 genotypes remain free from chronic transfusions for a median of 29 months
- Refined manufacturing process in HGB-207 yielded higher LentiGlobin DP VCNs and % transduced CD34+ cells
- All 3 patients with ≥ 6 months follow-up in HGB-207 have stopped RBC transfusions
  - Patients are maintaining Hb levels of 8.4 – 12.5 g/dL and have up to 10.5 g/dL vector-derived HbA^{T87Q}
- Safety profile in both studies is consistent with myeloablative conditioning with busulfan
  - No grade ≥ 3 AEs were considered related to LentiGlobin
- Longer follow-up and data in additional patients is necessary confirm the efficacy of LentiGlobin gene therapy for TDT

AE, adverse event; DP, drug product; Hb, hemoglobin; TDT, transfusion dependent β-thalassemia; VCN, vector copy number

HGB-204 (Northstar) and HGB-207 (Northstar-2) study sites and investigators

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