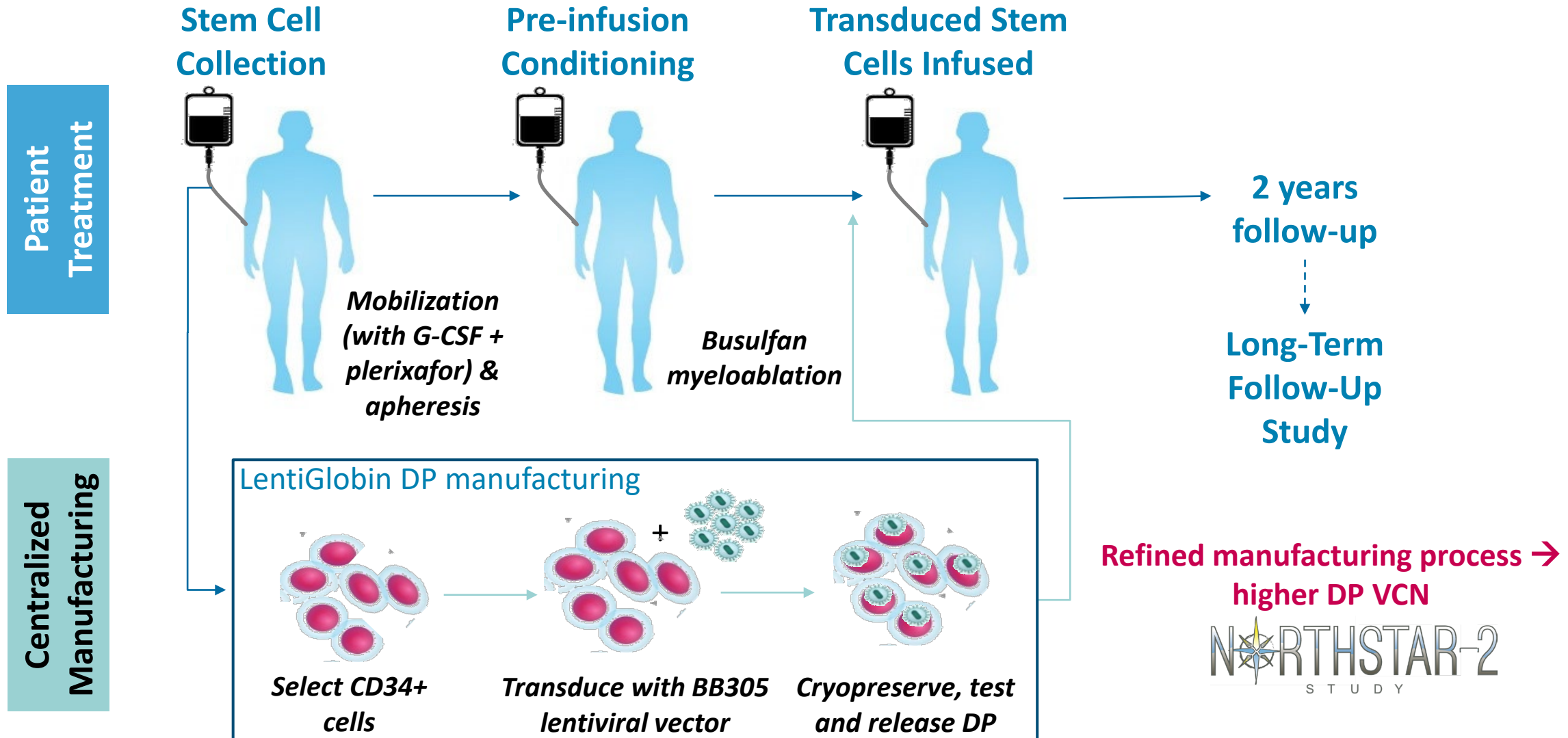


Safety and Efficacy of LentiGlobin Gene Therapy for Transfusion-Dependent β -thalassemia (TDT) in Patients with non- β^0/β^0 Genotypes: Interim Results from the HGB-204 (Northstar) and HGB-207 (Northstar-2) Trials

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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

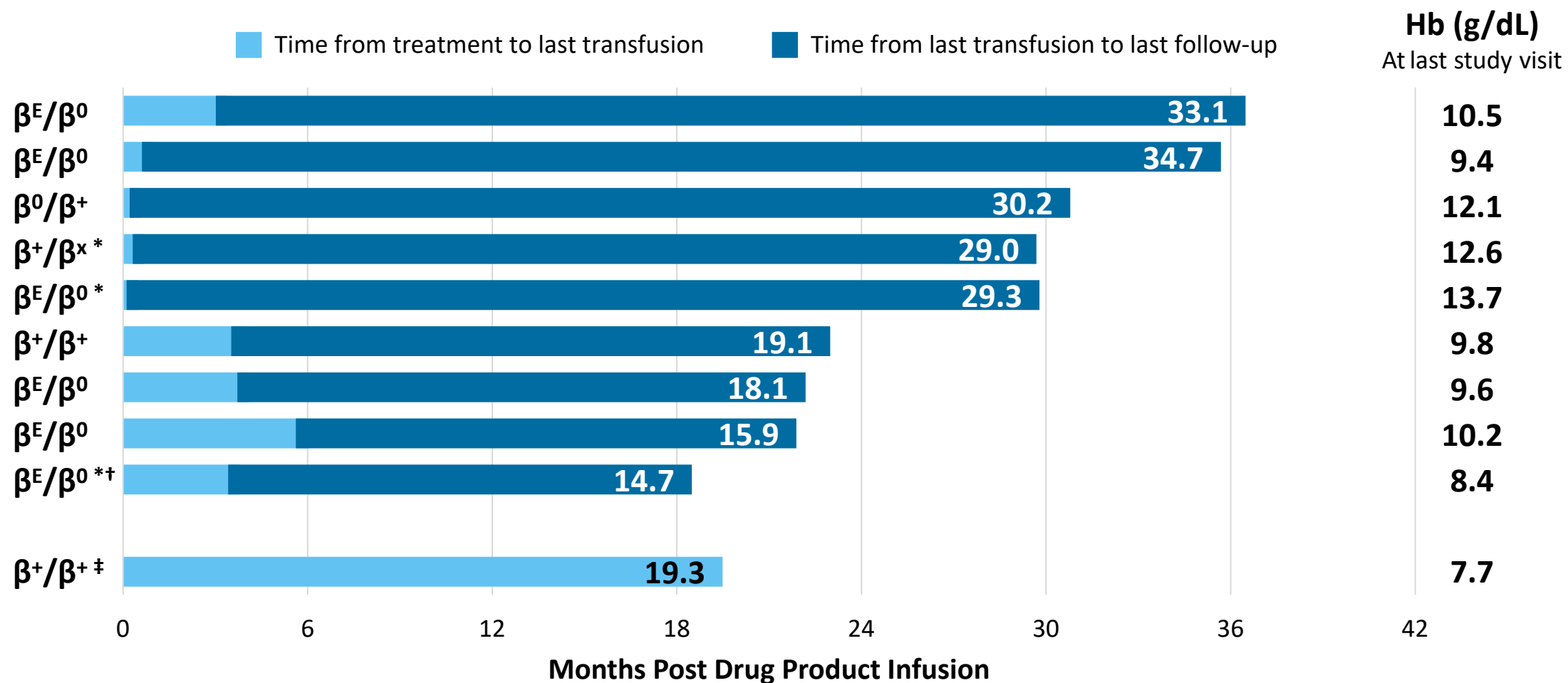
- International, multi-center, Phase 1/2, open-label, single-arm study in adolescents/adults with TDT
- Primary objectives: Safety and efficacy of LentiGlobin Drug Product in TDT
- **18 treated patients** (fully enrolled)
 - β^0/β^0 genotypes (n=8); Non- β^0/β^0 genotypes (n=10)
 - Ages: 18 – 35y (n=15),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

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

Data as of Sept 21, 2017

HGB-204: 9/10 patients with non- β^0/β^0 genotypes are free from chronic RBC transfusions

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

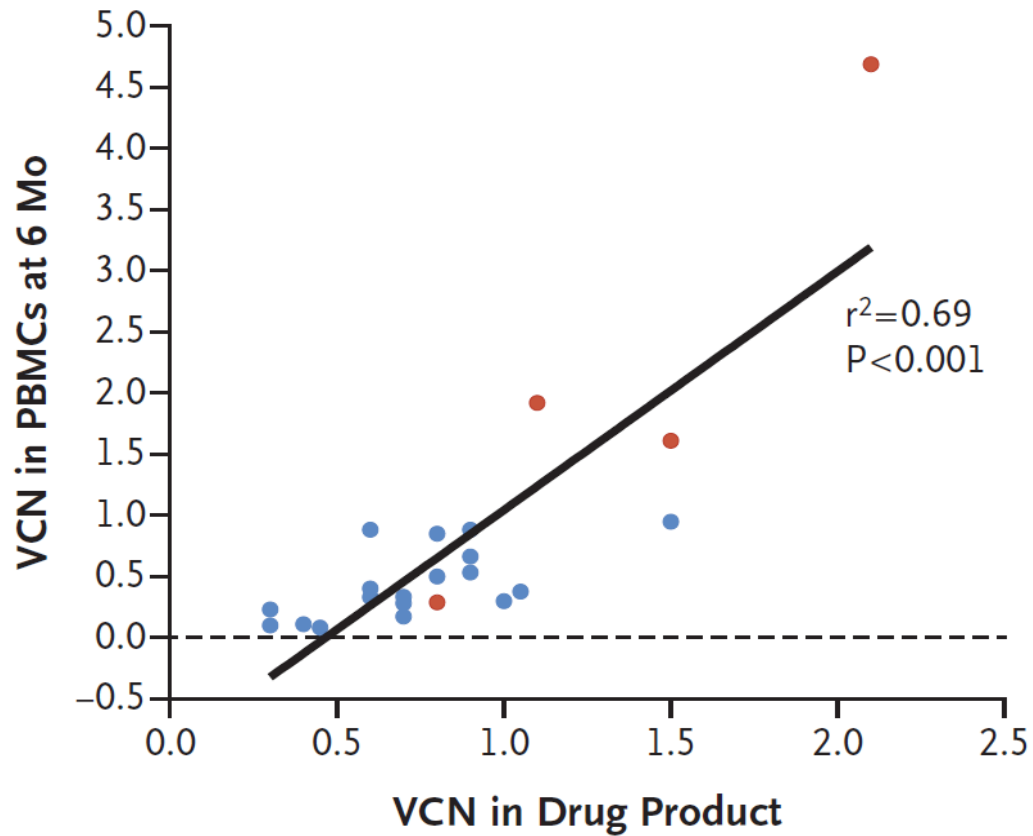


*Indicates male patients; †Patient received a single transfusion at Month 13 during an acute illness; ‡DP VCN of 0.3

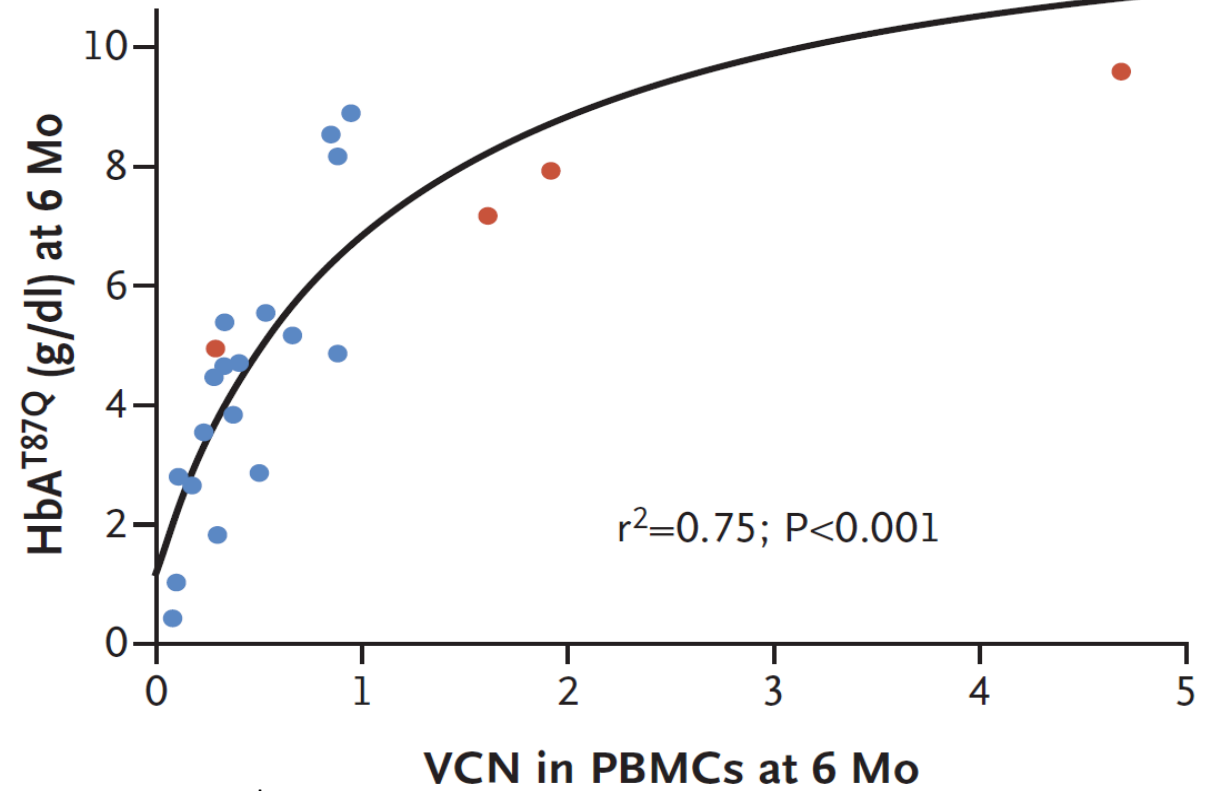
Peripheral VCN correlates with DP VCN and HbA^{T87Q} level at Month 6



Peripheral VCN vs. DP VCN



HbA^{T87Q} vs. Peripheral VCN



Blue: HGB-204; Red: HGB-205; DP, drug product; PBMC, peripheral blood mononuclear cells; VCN, vector copy number

HGB-207 (Northstar-2): Study disposition

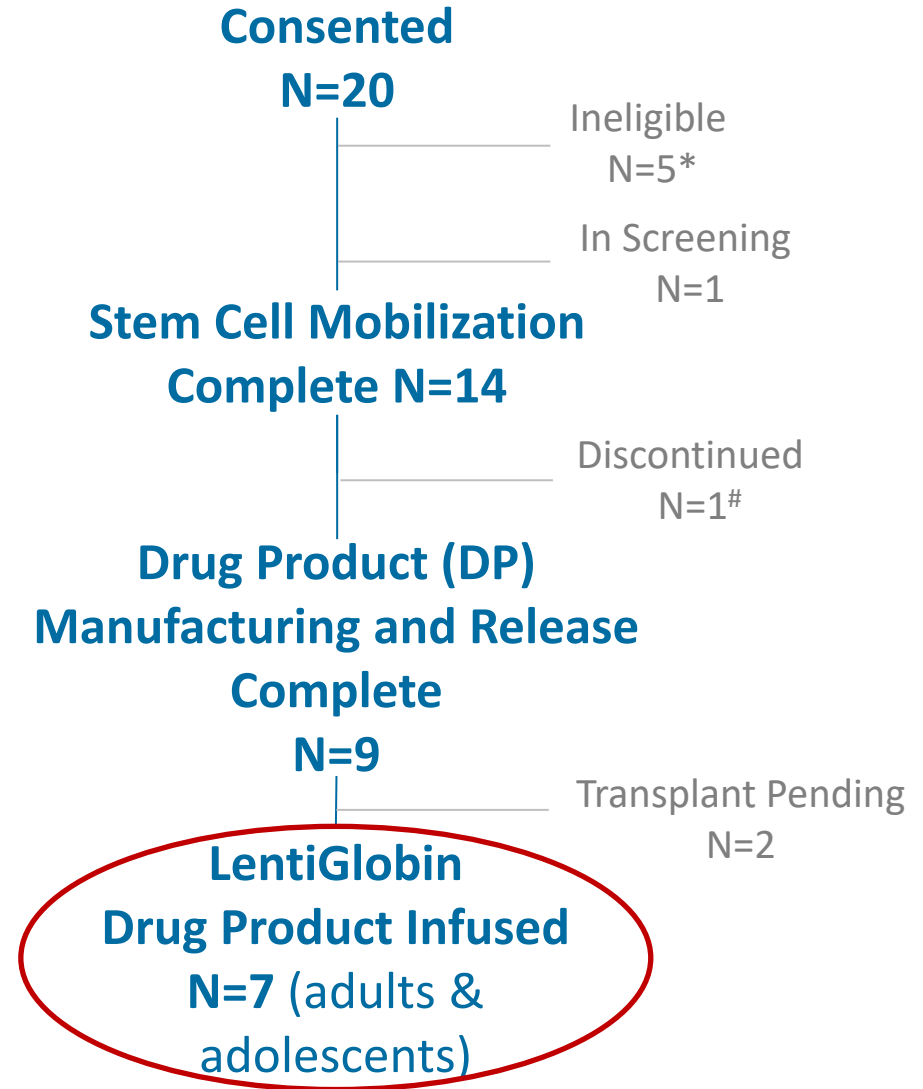
International, multi-center, Phase 3, open-label, single-arm study in adolescents/adults with TDT and a non- β^0/β^0 genotype

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

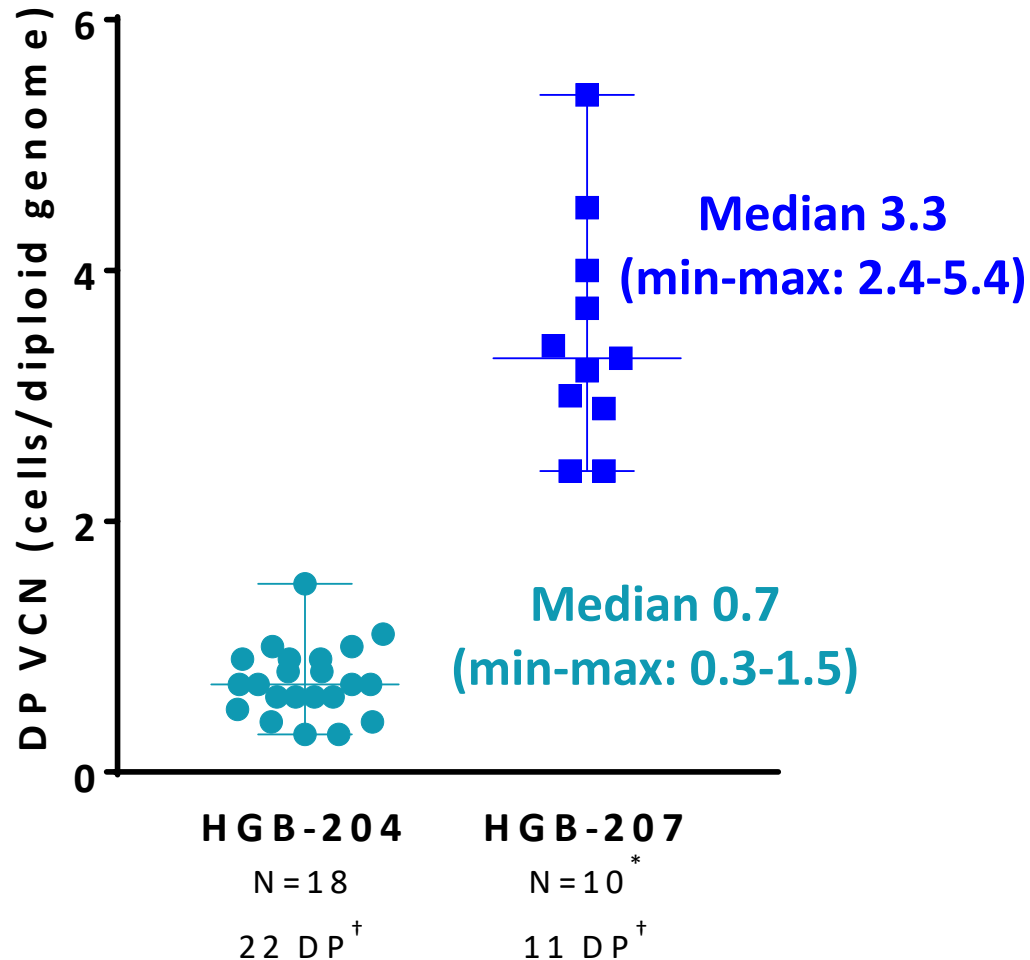
| | HGB-207 (N = 7) | HGB-204 (N = 10) |
|---|---------------------------------------|------------------------------|
| Drug product cell dose median (min–max), CD34+ cells $\times 10^6/\text{kg}$ | 7.9 (5.2 – 13.6) | 7.1 (5.2 – 13.0) |
| Busulfan AUC[†] median (min–max), $\mu\text{M} \cdot \text{min}$ | 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;

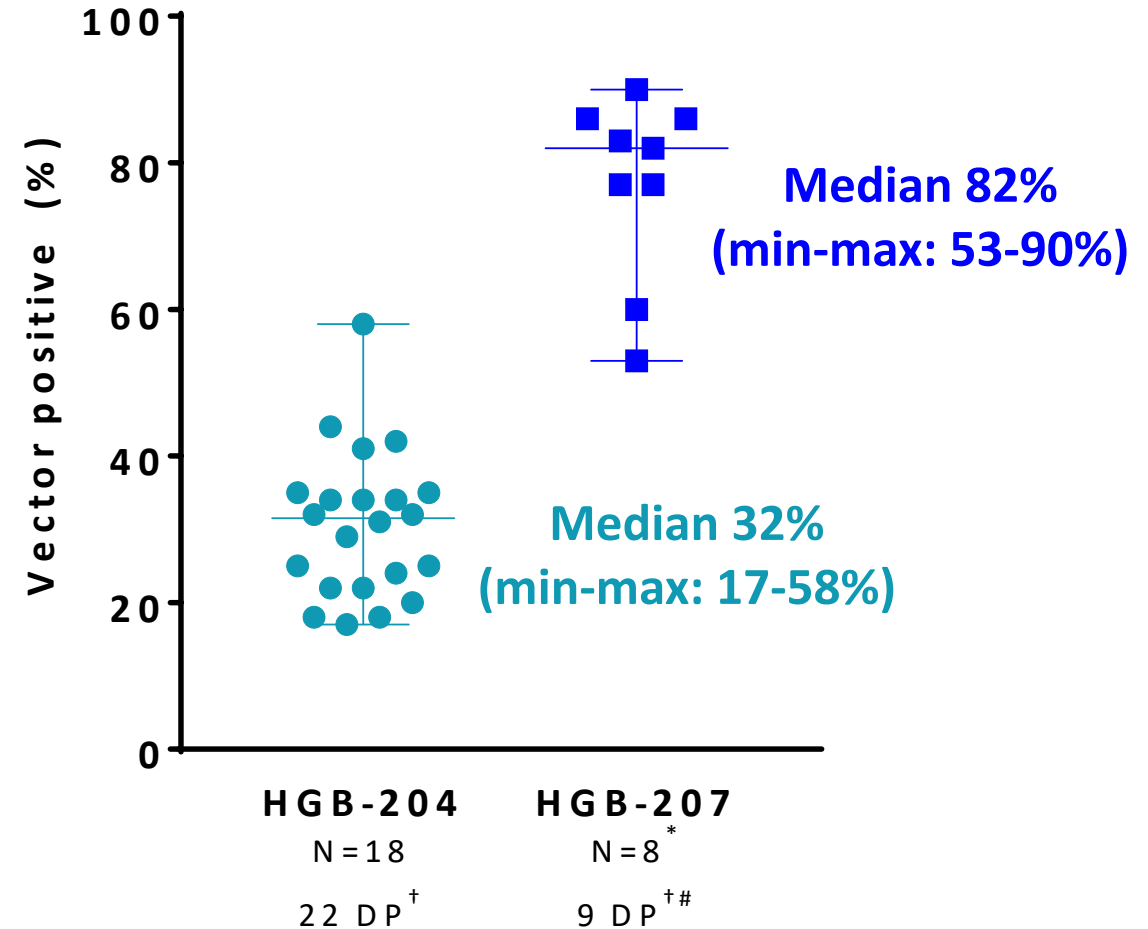
^{\#}Unsupported platelet count $\geq 20,000/\mu\text{L}$; ANC, absolute neutrophil count; AUC, area under the curve; DP, drug product; pRBC, packed red blood cells; TDT, transfusion-dependent β -thalassemia.

Refined manufacturing process yielded improved drug product characteristics

Vector copy number (VCN) in drug product



Proportion of CD34+ cells transduced

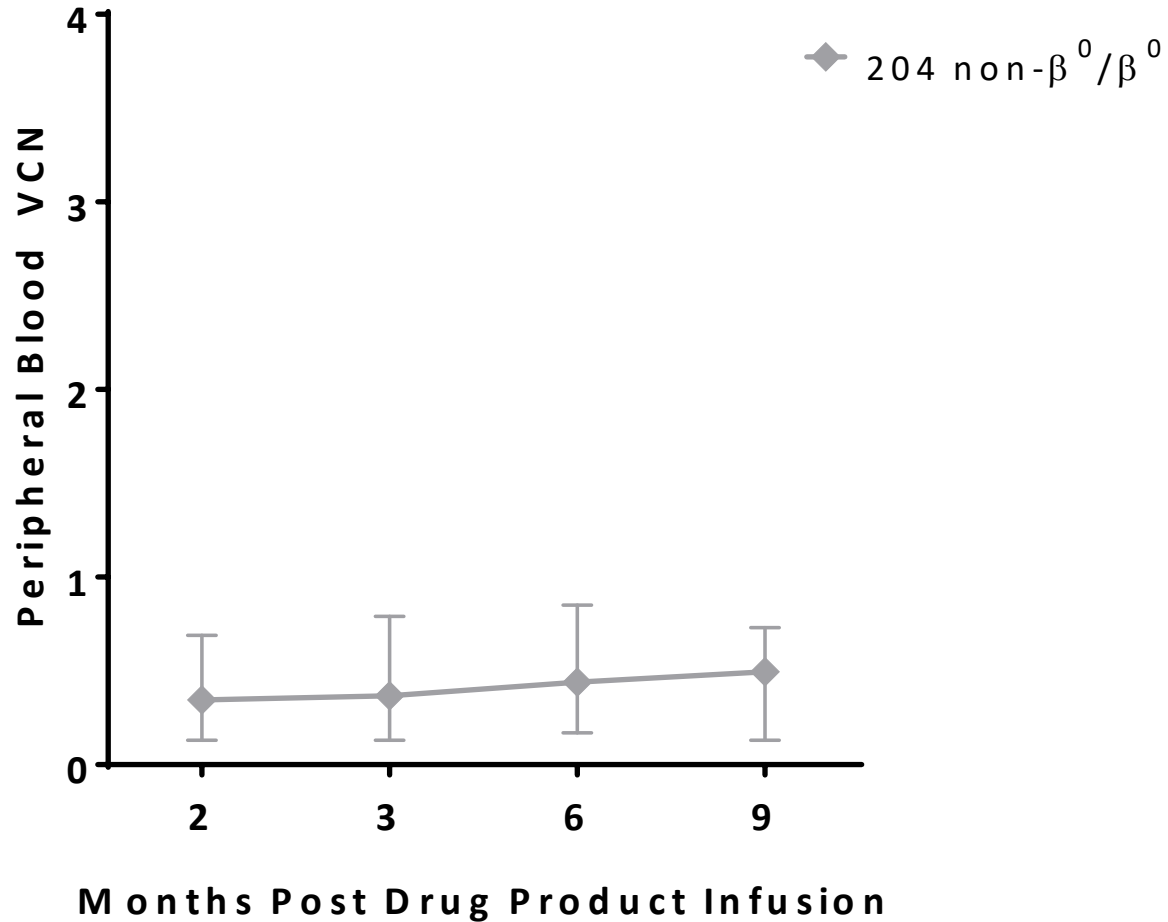


*As of Oct 13, 2017 in the 7 treated patients, the median DP VCN was 3.1 (min – max: 2.4 – 4.0) and the median % CD34+ cells transduced was 77% (min – max: 53 – 90);

[†]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

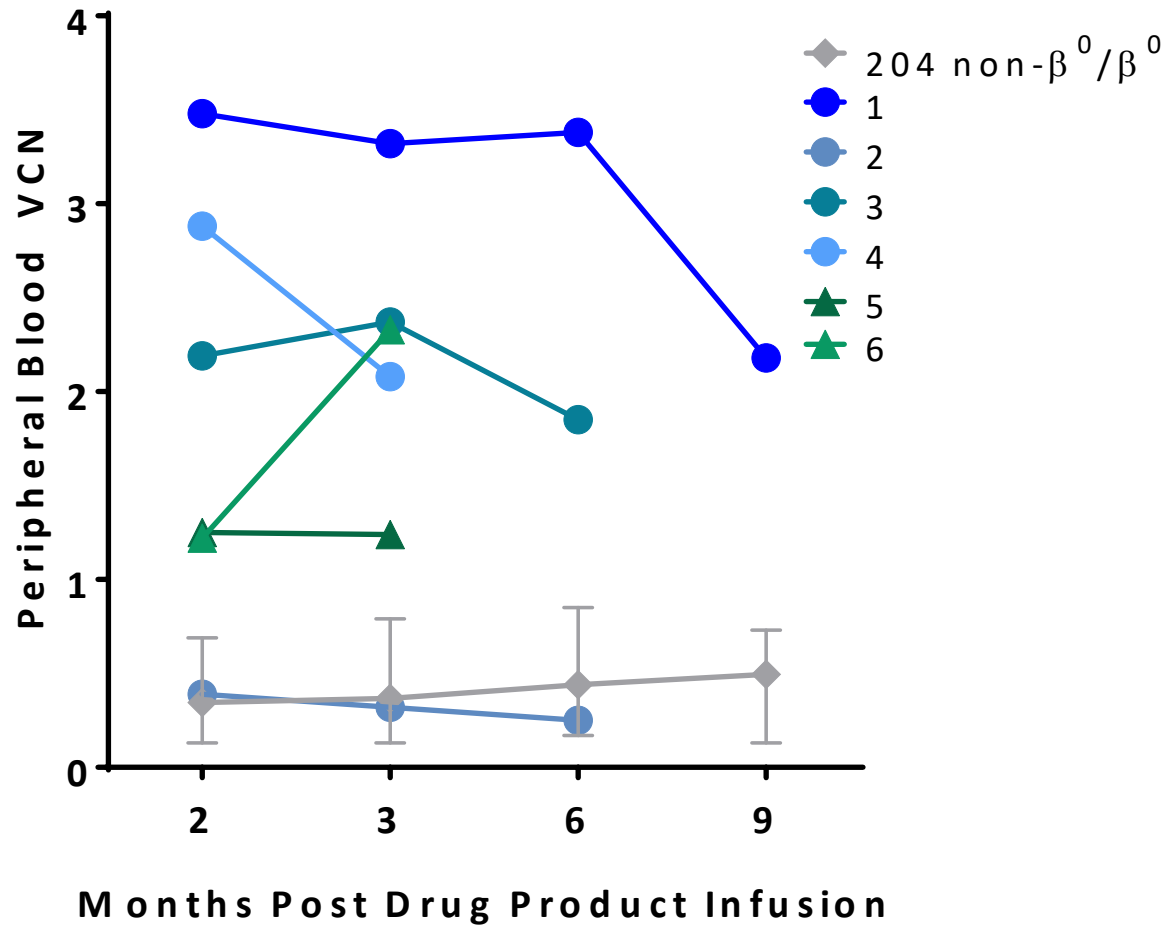
Peripheral blood VCN



For 204 non-β⁰/β⁰ pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

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

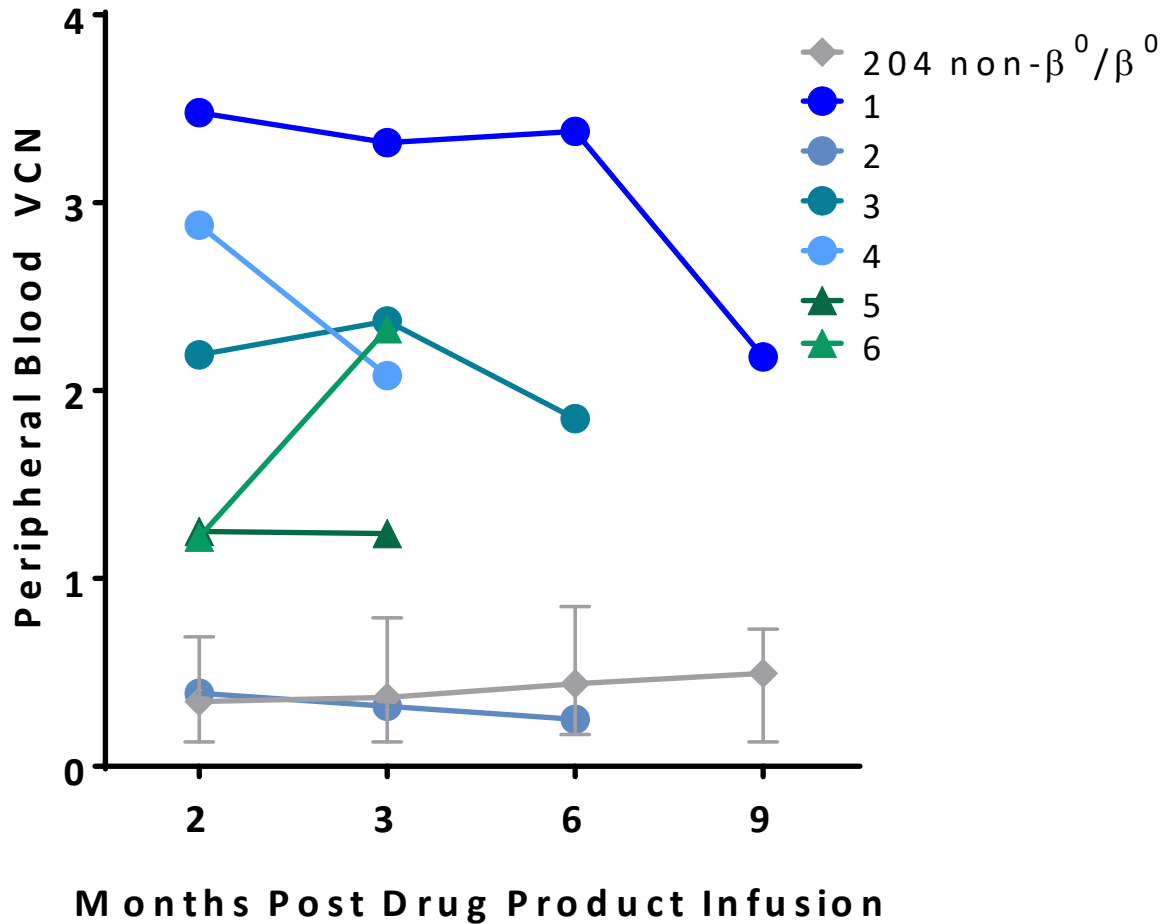
Peripheral blood VCN



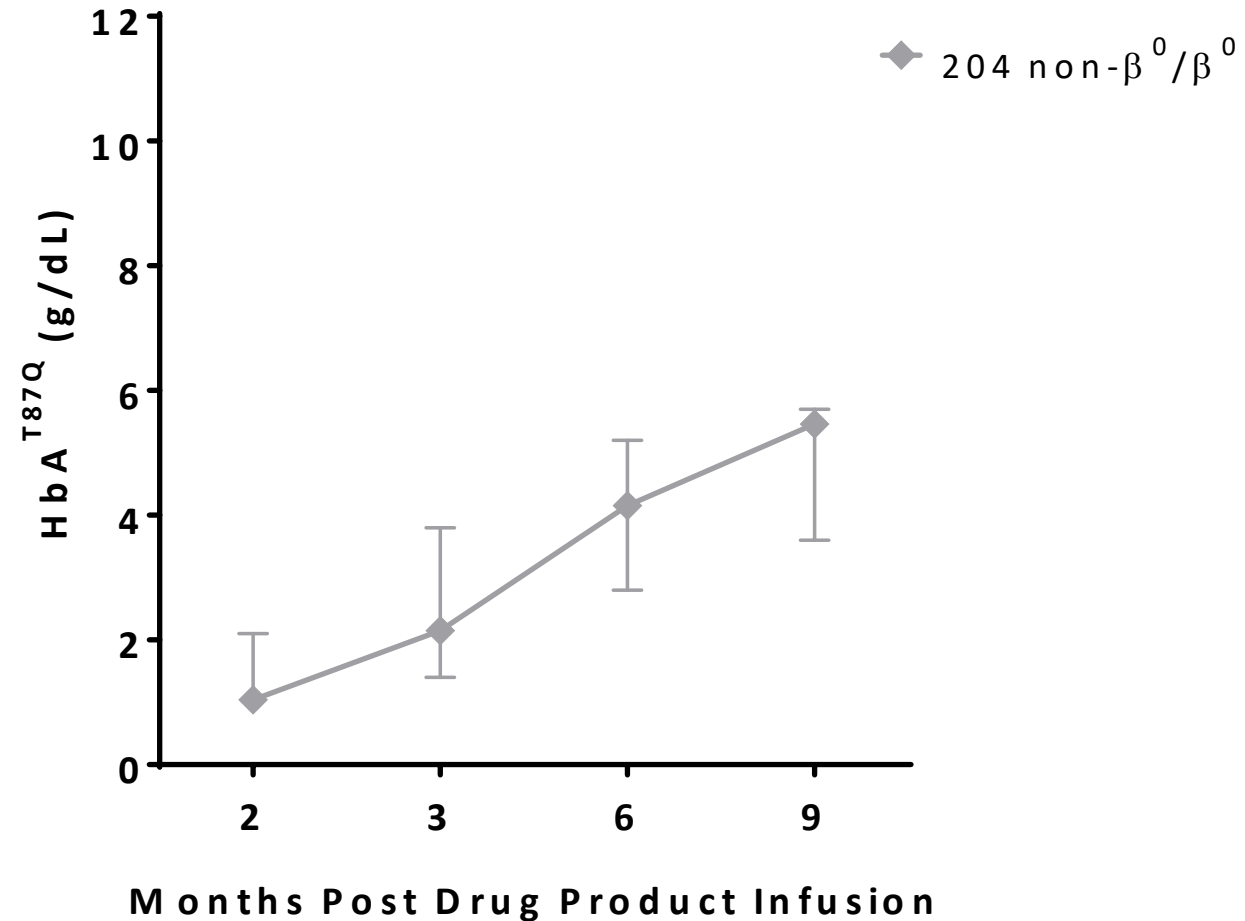
For 204 non-β⁰/β⁰ pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

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

Peripheral blood VCN



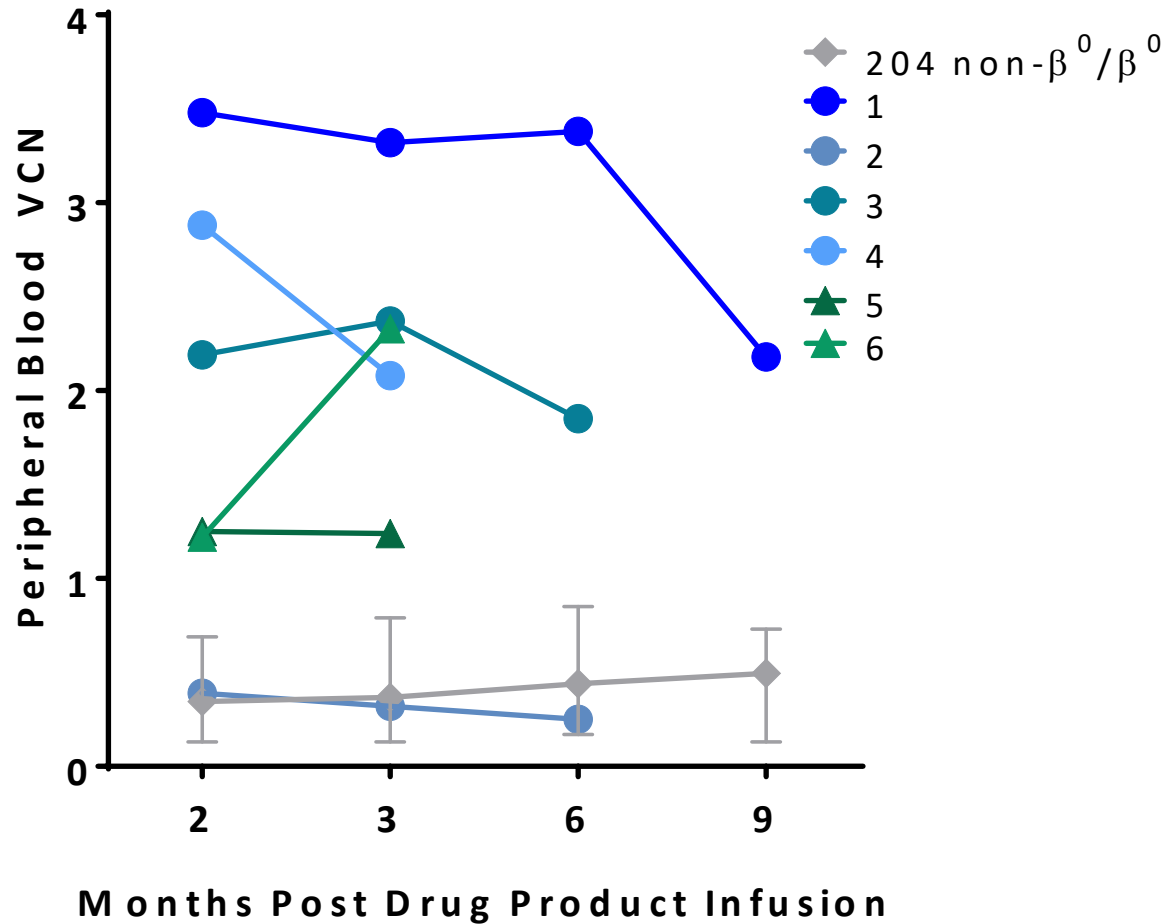
HbA^{T87Q}



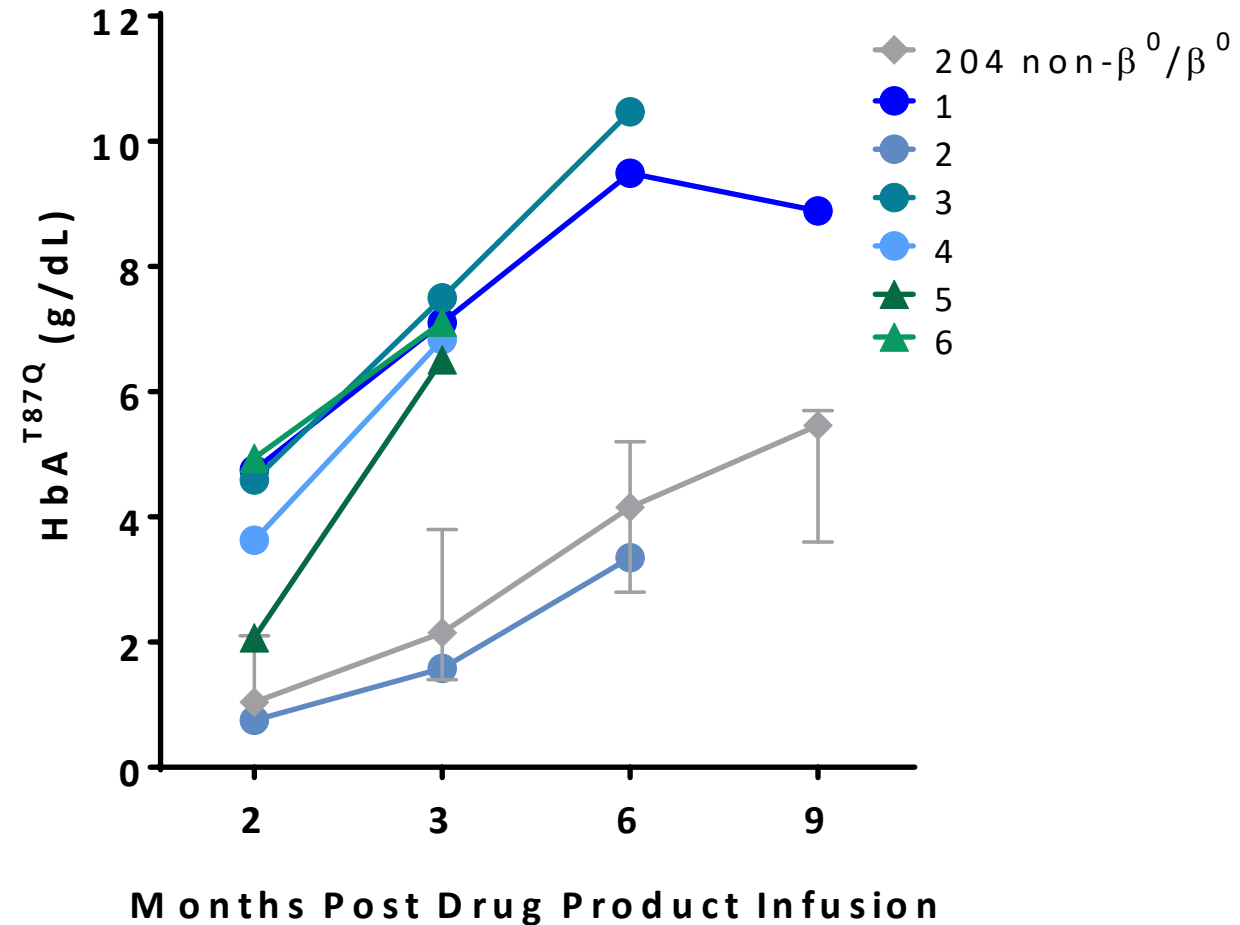
For 204 non- β^0/β^0 pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

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

Peripheral blood VCN

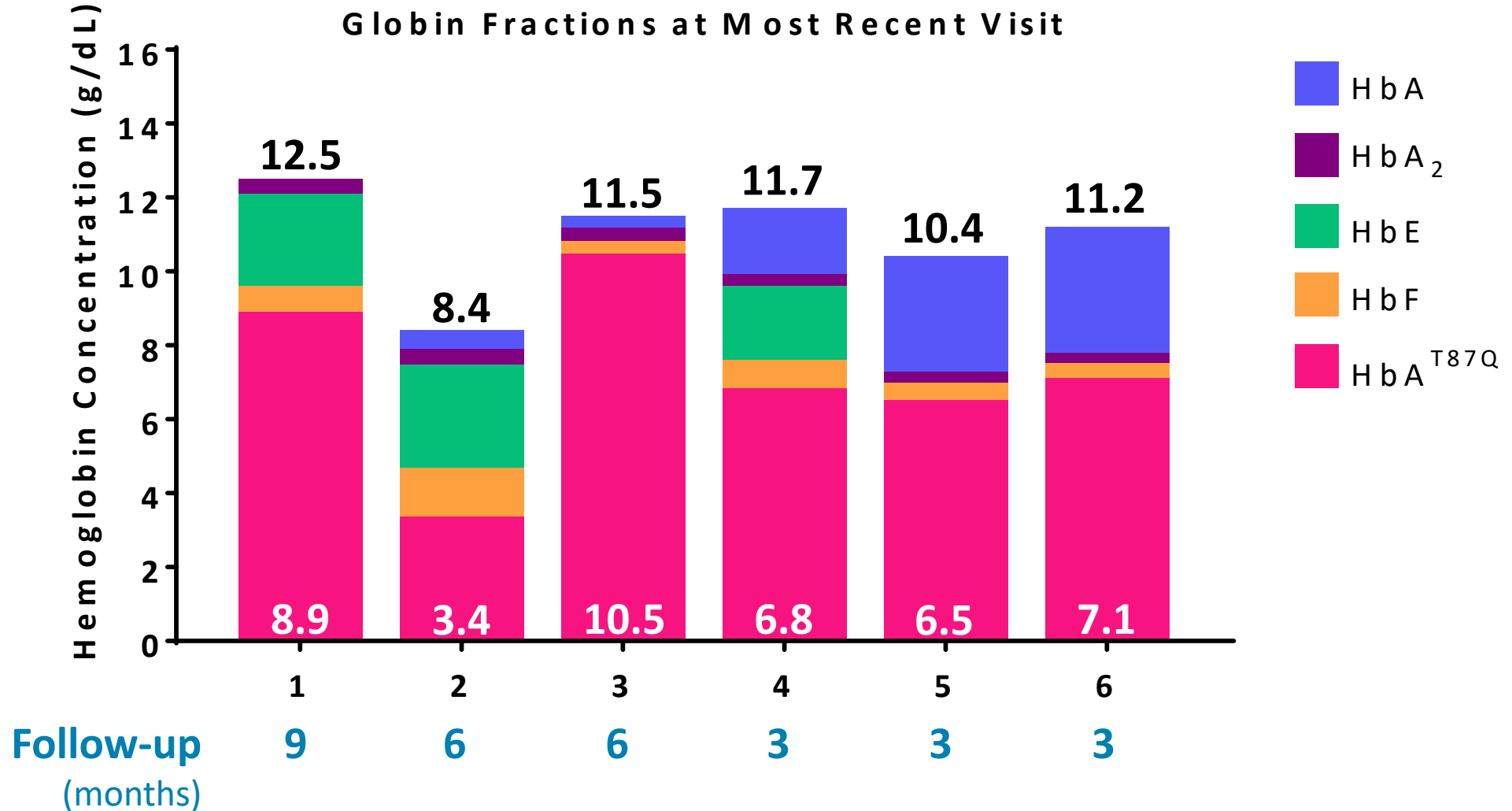


HbA^{T87Q}



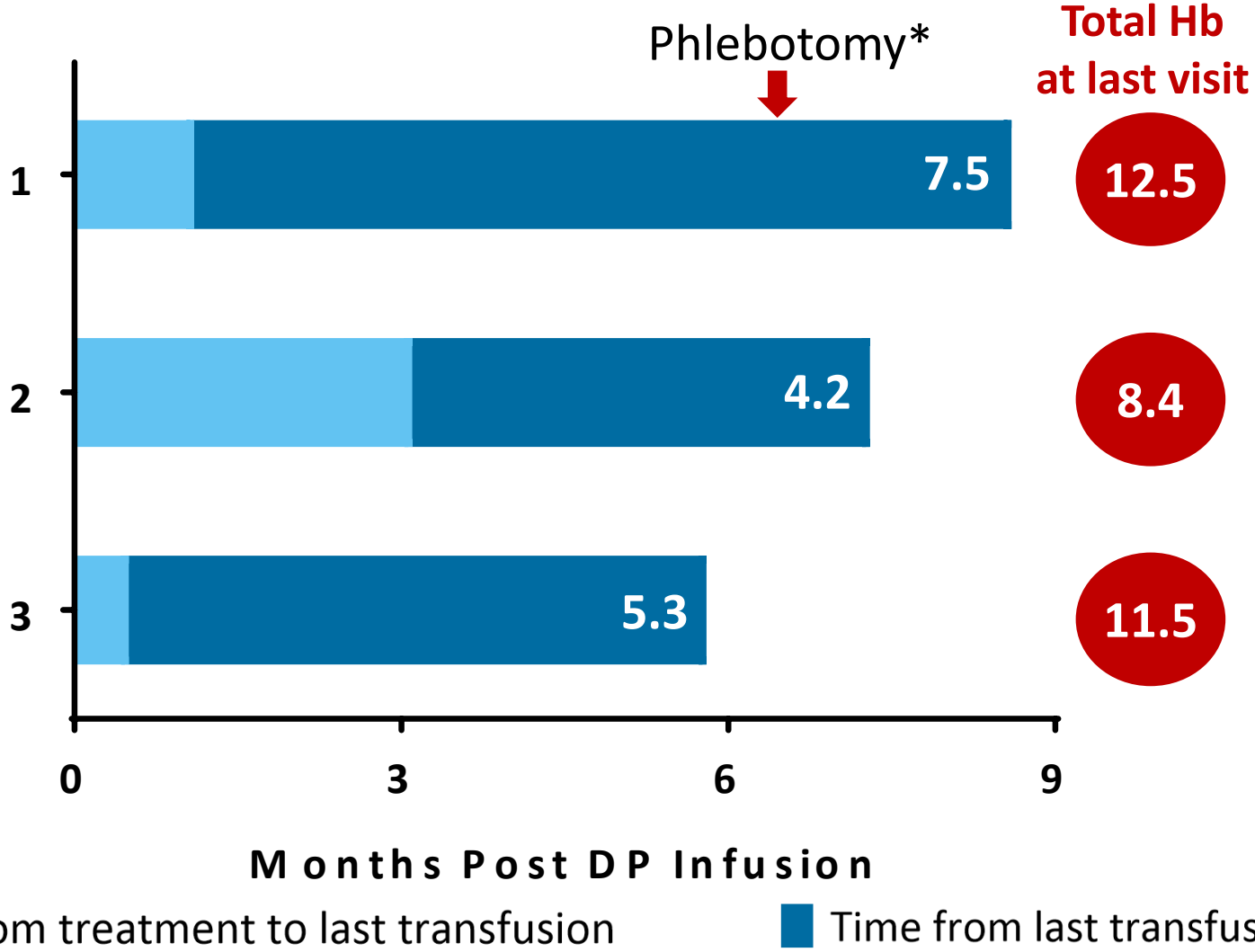
For 204 non- β^0/β^0 pts, medians (Q1, Q3) depicted; Circles indicate female, triangles indicate male

HGB-207: 5 of 6 patients making at least 6 g/dL of HbA^{T87Q} at ≥3 months



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

HGB-207: Patients with ≥ 6 months follow-up have 4 – 7 months without RBC transfusion



*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 <i>DP infusion to up to 2 years of follow-up</i> | Patient Incidence n (%) |
|--|----------------------------|
| Stomatitis | 8 (80) |
| Febrile neutropenia | 6 (60) |
| Irregular menstruation | 2 (20) |
| Pharyngeal inflammation | 2 (20) |
| Serious AEs <i>DP infusion to last follow-up</i> | |
| 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 <i>DP infusion to last follow-up</i> | Patient Incidence n (%) |
|--|----------------------------|
| Stomatitis | 3 (43) |
| ALT increase | 2 (29) |
| Serious AEs <i>DP infusion to last follow-up</i> | |
| Transfusion reaction | 1 (14) |
| Hypotension | 1 (14) |

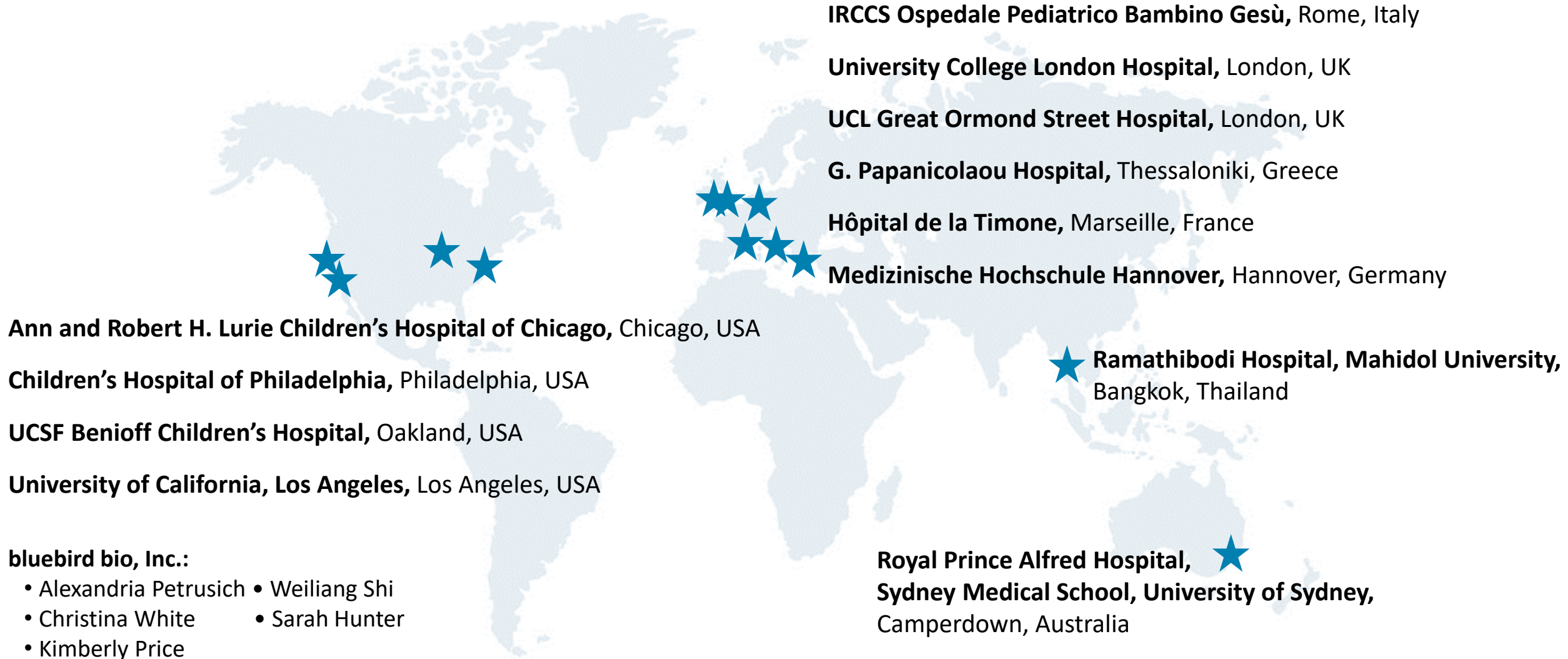
- No grade ≥ 3 DP-related AEs
- No graft failure and no deaths
- No replication competent lentivirus
- No evidence of clonal dominance

*AEs are presented for patients with TDT and non-β⁰/β⁰ genotypes; †Hematologic AEs commonly observed post-transplant have been excluded.
AEs, adverse events; 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 are needed to definitively validate these promising results of LentiGlobin gene therapy for patients with TDT and non- β^0/β^0 genotypes
- The phase 3 HGB-212 study is currently recruiting patients with TDT and β^0/β^0 genotypes to evaluate LentiGlobin gene therapy

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



Thank you to the study participants and their families