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LentiGlobin™ Gene Therapy for Transfusion-Dependent β-Thalassemia: Update from the Northstar HGB-204 Phase 1/2 Clinical Study

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Disclosures

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- Board Membership: none
- Equity Ownership: none

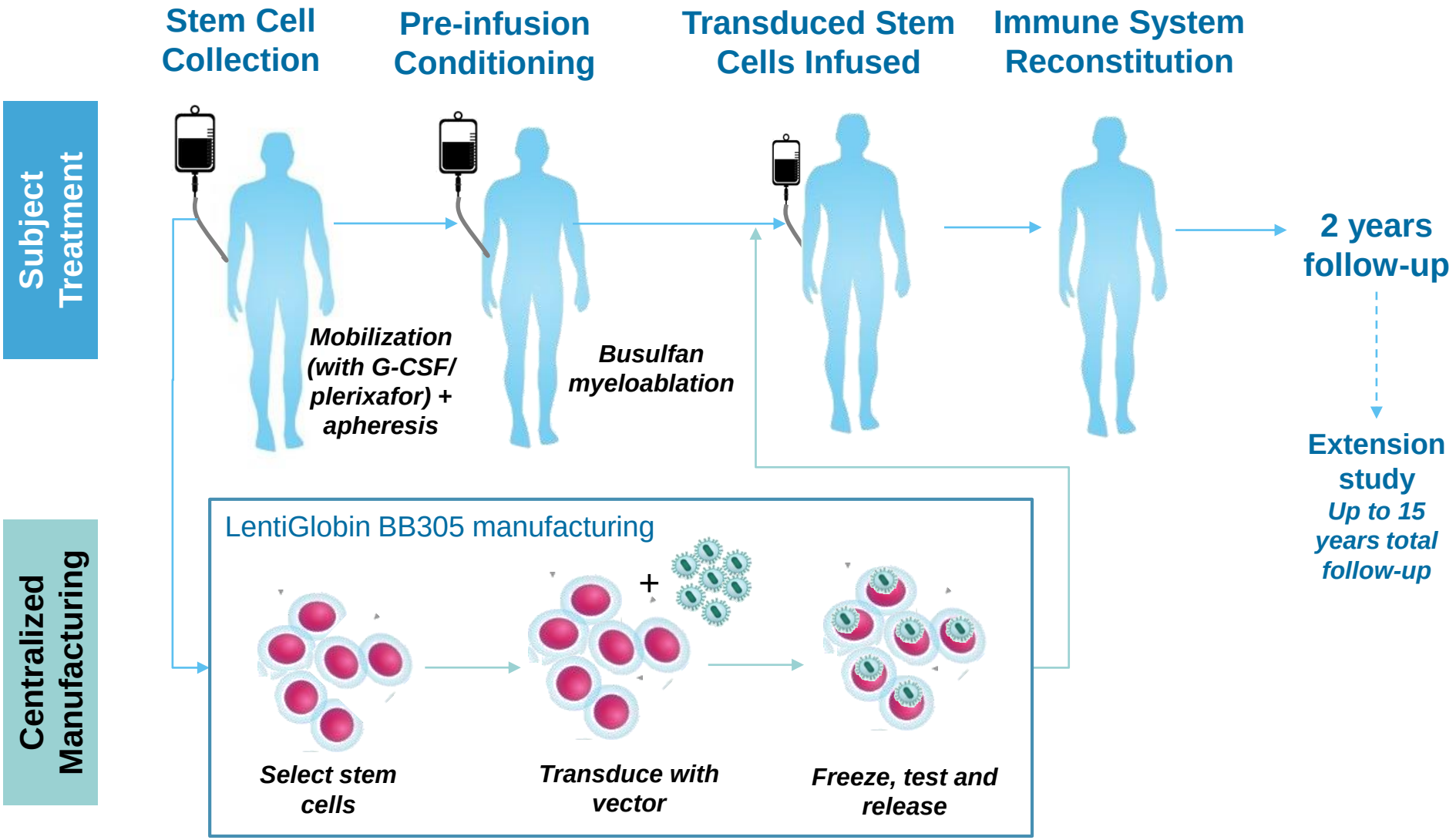
Northstar (HGB-204) study of LentiGlobin BB305 gene therapy in TDT

- International, multi-center, Phase 1/2, open-label, single-arm study in adolescents/adults with TDT
- Primary objectives: Safety and efficacy of LentiGlobin BB305 Drug Product in transfusion-dependent β-thalassemia (TDT)
- 18 treated patients (fully enrolled)
  - Ages 18-35y (N=15), 12-17y (N=3)
  - Transfusion dependence: ≥8 red blood cell (pRBC) transfusions/year or ≥100mL/kg/year in the 2 years before enrollment

Status

All 18 patients have ≥ 6 months follow-up
2 patients have completed 2-year analysis

Overview of the HGB-204 clinical protocol



Patient and drug product characteristics

N=18 treated patients

	Genotype	
	β^0/β^0 (n=8)	**Non-β^0/β^0** (n=10)
Genotype	8	
β^E/β^0		6
Other (β^+/β^0, β^+/β^+, β^x/β^0)		4
Age at start of regular transfusions *median (range) years*	0 (0 – 7)	6 (0 – 26)
Age at consent *median (range) years*	23 (12 - 35)	19.5 (16 - 34)
Median (range) pre-study pRBC transfusion vol. *annualized median (range) mL/kg/year*	184.9 (128.7 - 261.3)	146.3 (117.0 – 234.5)
Splenectomy	3	3
Drug Product Parameters	Median (range)	
Drug product VCN[1]	0.7 (range 0.3 - 1.5)	0.8 (range 0.3 - 1.1)
Drug product cell dose *CD34+ cells x10^6/kg*	11.0 (range 6.1-18.1)	7.1 (range 5.2-13.0)

1. VCN: vector copy number (vector copies per diploid genome)

Transplant summary and gene therapy-related safety *N=18 treated patients*

	Median (range)
Follow-up, months	**17.0** (6.3-29.8)
Neutrophil engraftment, study day[1]	**18.5** (14 - 30)
Platelet engraftment, study day[2]	**39.5** (19 - 191)

- No serious bleeding complications before platelet engraftment
- No confirmed replication competent lentivirus
- Highly polyclonal vector integration
  - No evidence of clonal dominance per integration site analysis

1. ANC ≥ 500 for three consecutive days. 2. Unsupported platelet count ≥ 20,000/µL.

Safety summary

N=18 treated patients

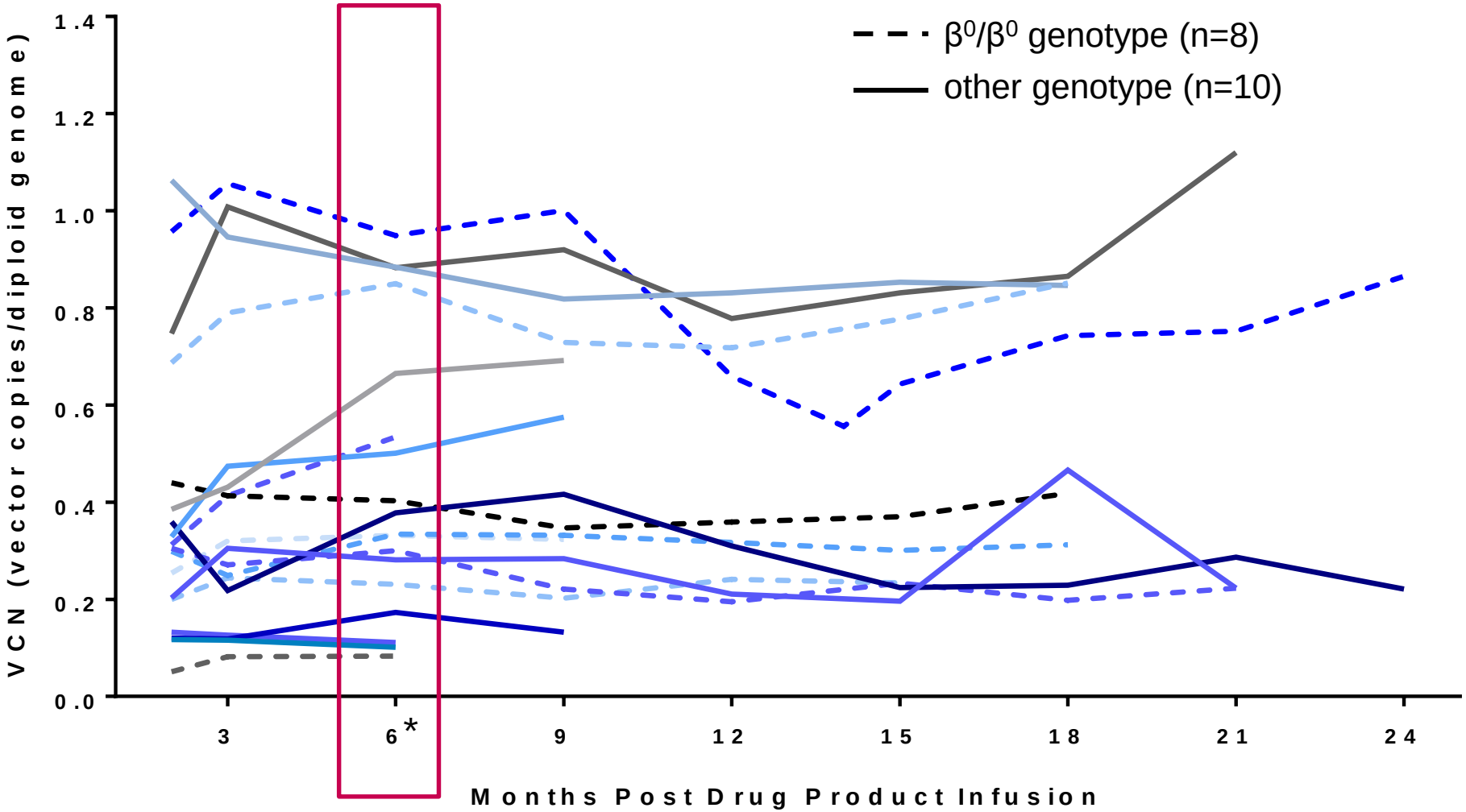
Non-laboratory[1] Grade ≥3 non-serious AEs reported in ≥2 patients	Incidence[2]
Stomatitis	12
Febrile neutropenia	10
Pharyngeal inflammation	5
Epistaxis	2
Fever	2

All Serious AEs	Incidence[2]
Veno-occlusive liver disease (Grade 3)	2
Appendicitis (Grade 3)	1
Cellulitis (Grade 3)	1
Thrombosis in central catheter (Grade 2)	1
Intracardiac thrombus (Grade 3)	1

- Six Grade 1 adverse events (AEs) related or possibly related to LentiGlobin

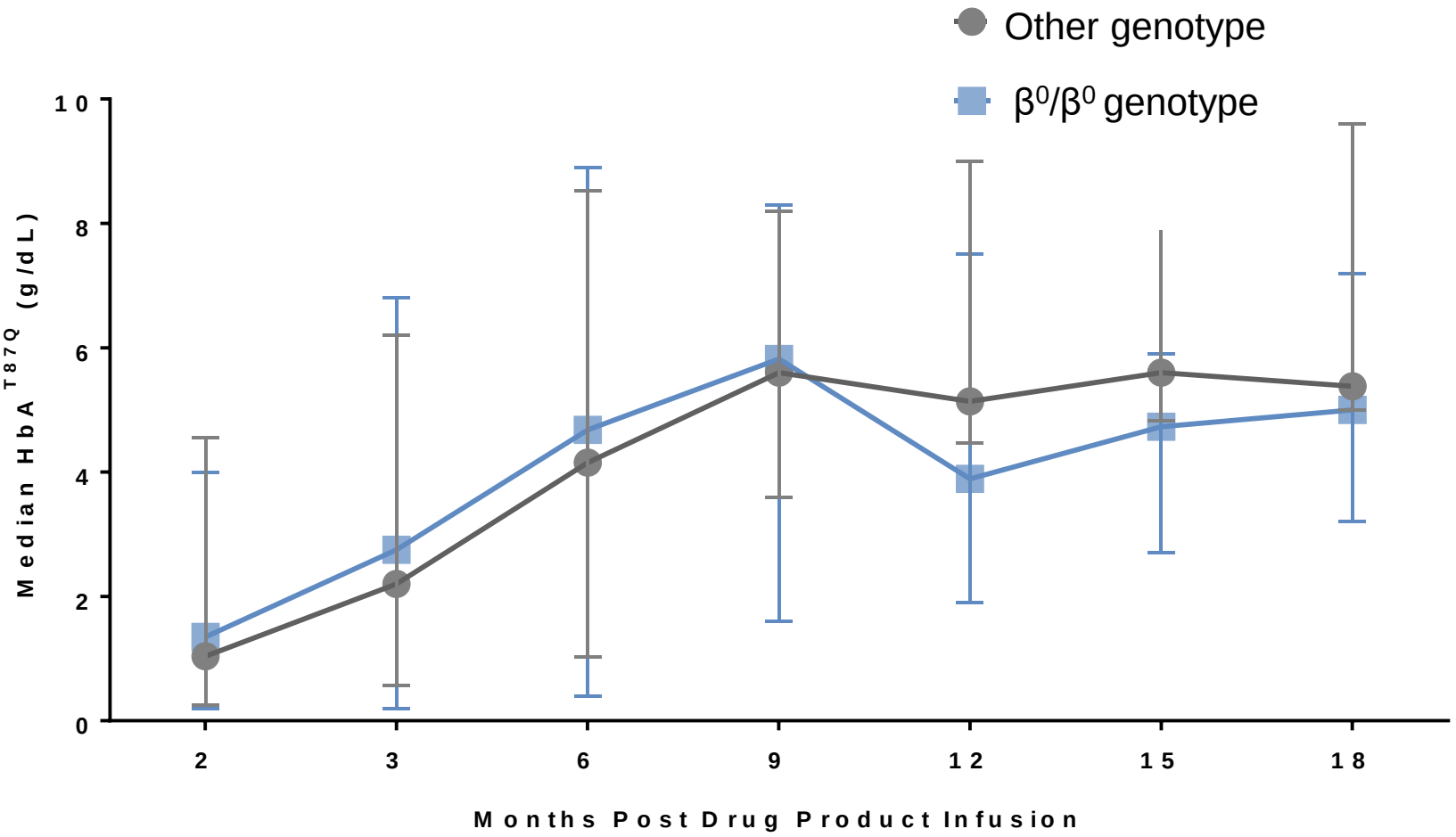
1. Hematologic laboratory parameters commonly abnormal post-transplant have been excluded from this table
2. Incidence from start of conditioning (Day -8) to data cut-off

VCN in peripheral blood over time



*Median peripheral VCN at month 6: β^0/β^0 genotype 0.3 [range 0.1-1.0]; other genotype 0.4 [range 0.1-0.9]

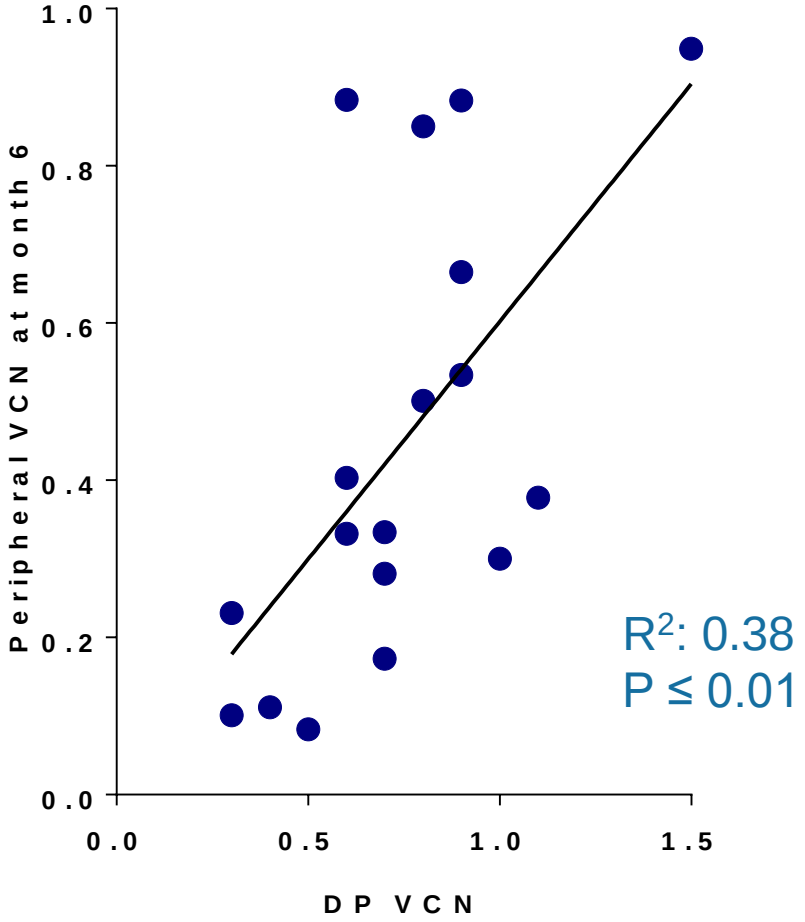
HbA^{T87Q} production increases to month 9, then stabilizes



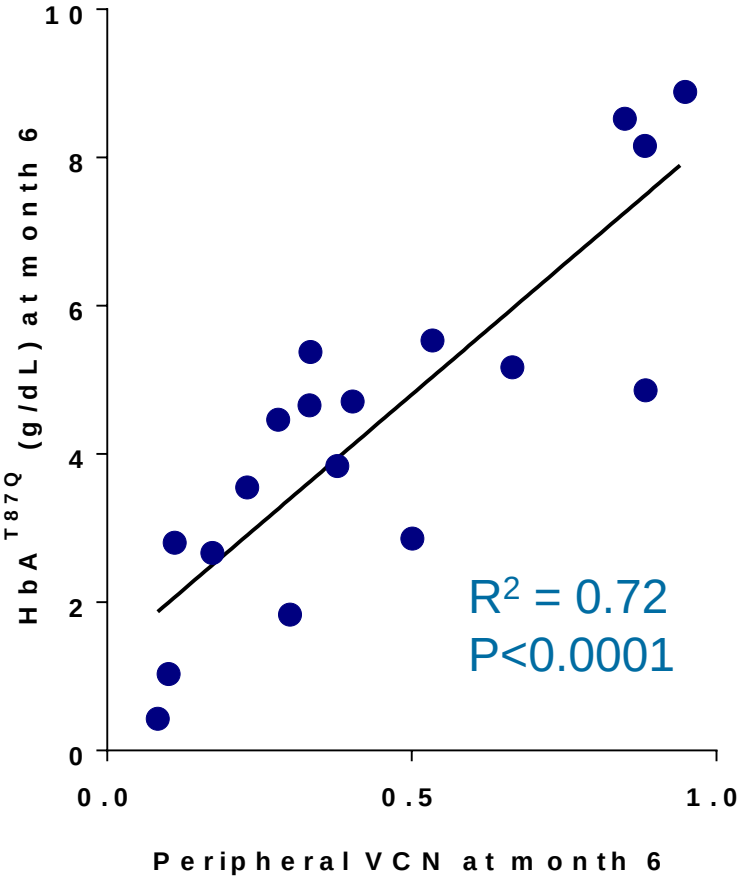
N:	**18**	**18**	**18**	**14**	**10**	**10**	**8**
Median (g/dL)	**1.1**	**2.6**	**4.6**	**5.6**	**4.9**	**5.1**	**5.4**

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

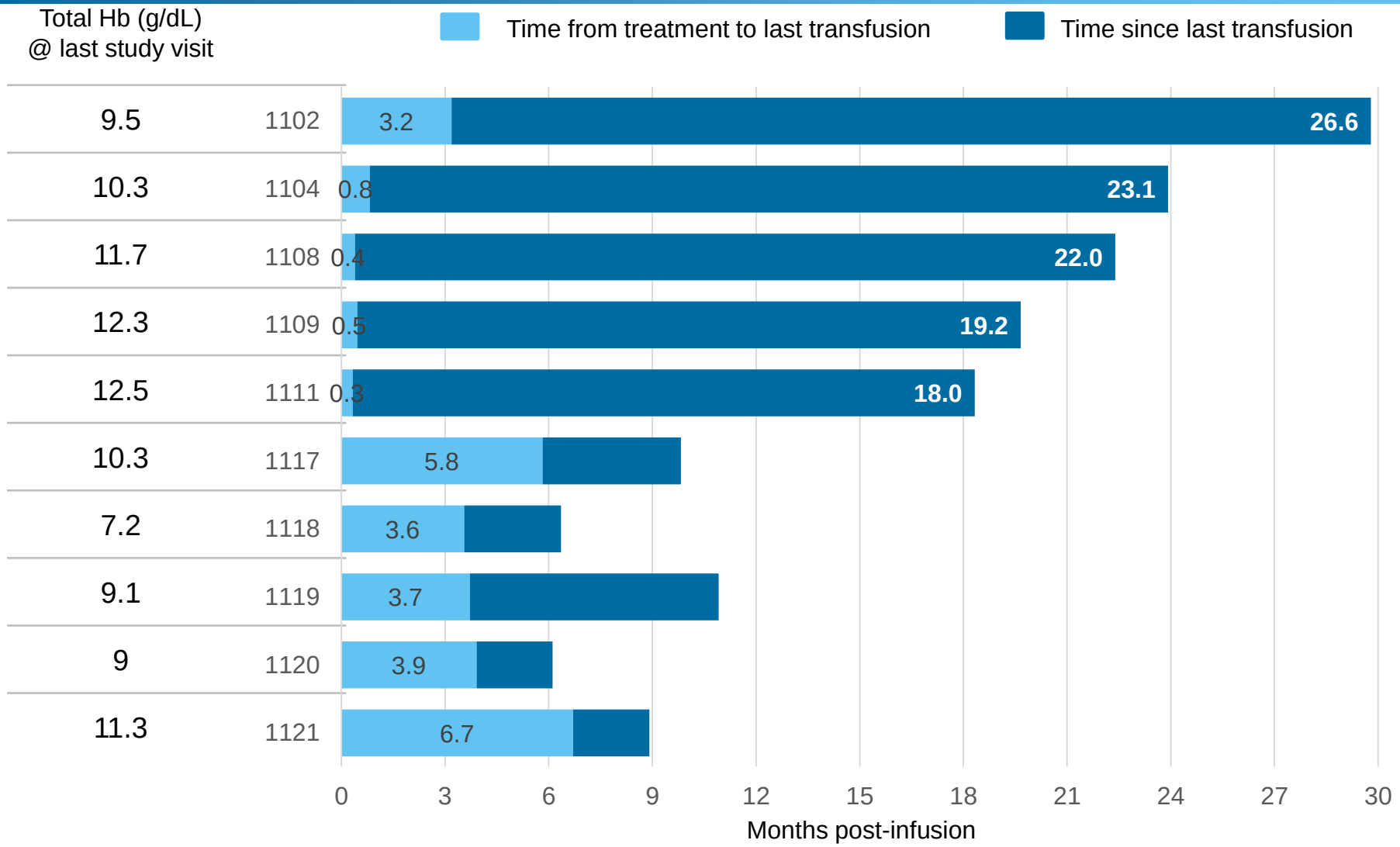
Peripheral VCN vs. DP VCN



HbA^{T87Q} vs. Peripheral VCN



Patients with non-β^0/β^0 genotypes and ≥1 year follow-up have 18 to 27 months since last RBC transfusion

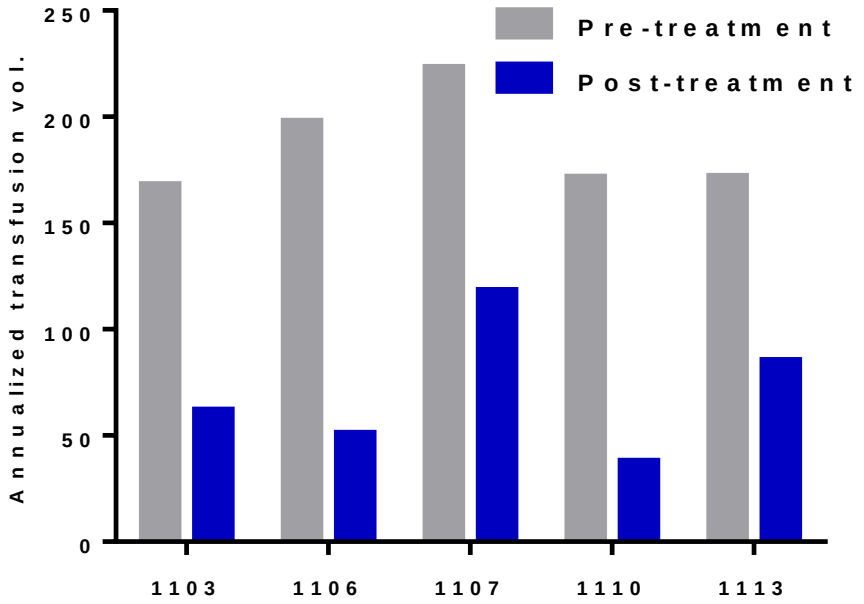


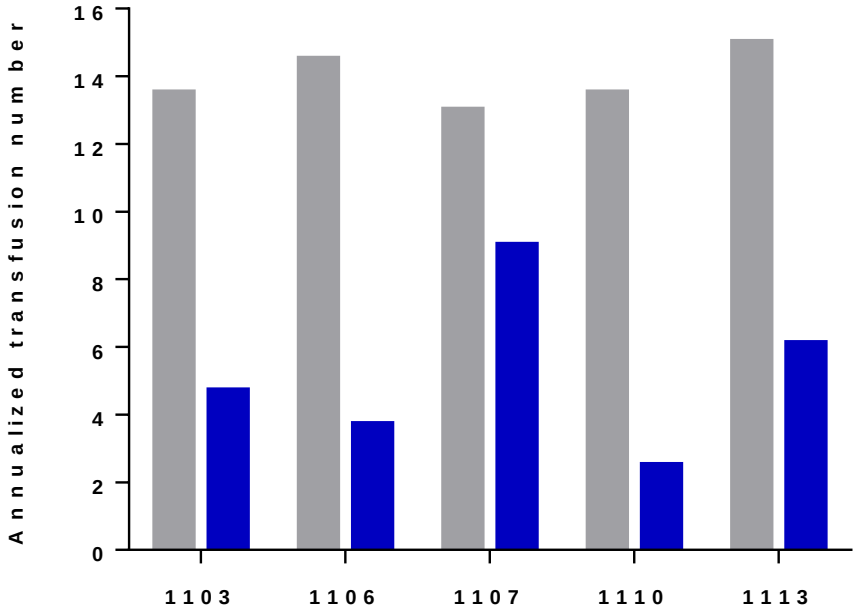
Median follow-up for patients with non-β^0/β^0 genotypes (N=10) 14.7 months (range 6.3-29.8)

Reduction in RBC transfusion requirements in patients with β^0/β^0 genotypes with ≥12 months follow-up

63%
Median Reduction in Transfusion Volume
(range 47%-78%)

65%
Median Reduction in Number of Transfusions
(range 31%-81%)

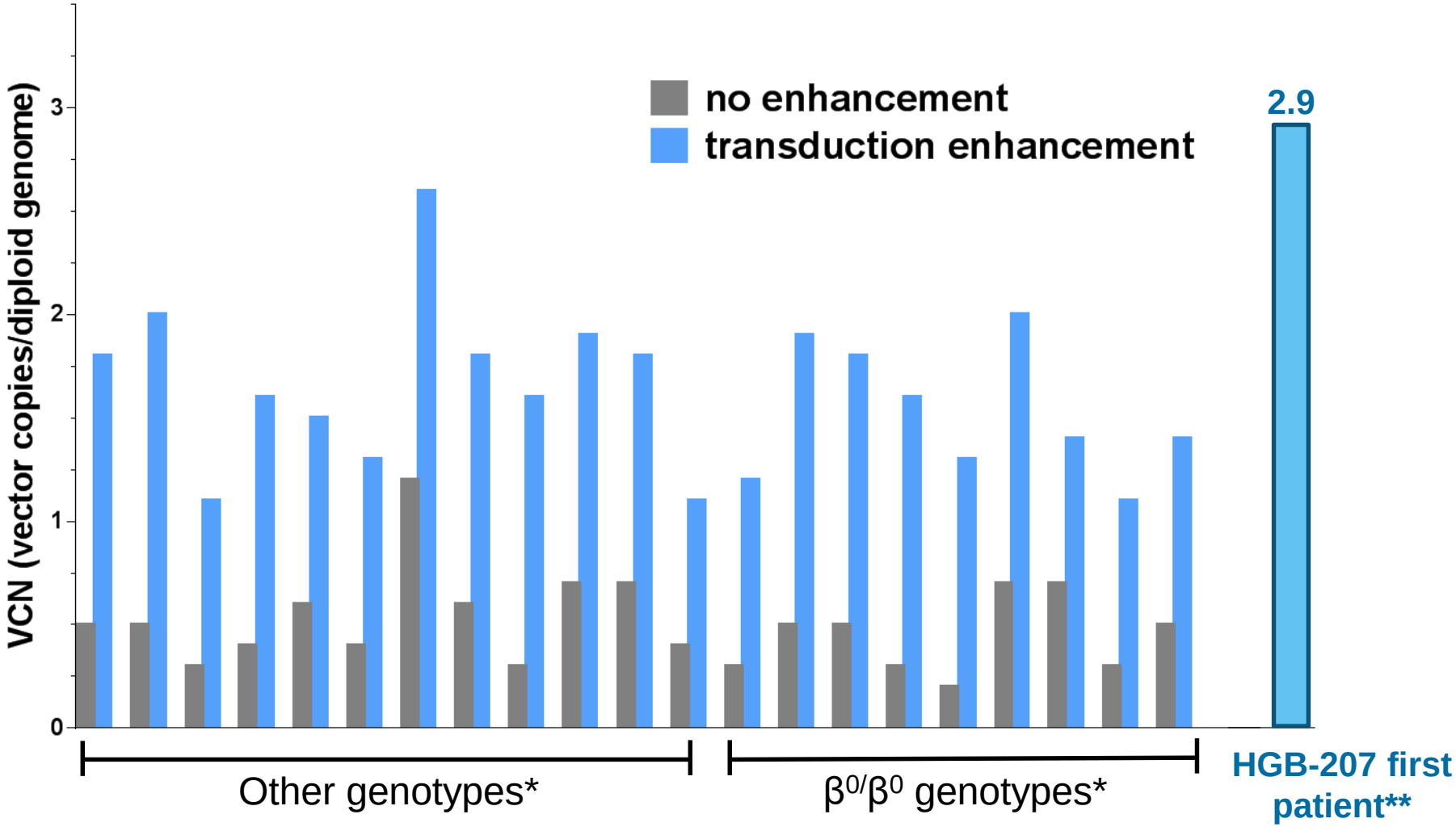




Post-treatment: annualized on-study volume and number of transfusions based on observed values starting at month 6 through data cut-off

Median follow-up for patients with β^0/β^0 genotypes (N=8) 17.3 months (range 6.7-25.4)

Transduction enhancement increases drug product VCN



*Exploratory *in vitro* analysis conducted at research scale with retained CD34+ cells from HGB-204 **GMP manufacturing

Next steps: Pivotal clinical studies of LentiGlobin therapy in TDT

NORTHSTAR-2 STUDY

HGB-207

Non-β^0/β^0 genotypes

Phase 3, multi-center, global study

- N=15 adults and adolescents, and N=8 pediatric patients
- **Open and enrolling**

NORTHSTAR-3 STUDY

HGB-212

β^0/β^0 genotypes

Phase 3, multi-center, global study

- N=15 adults, adolescents and pediatric patients
- **Initiation planned for 2017**

Summary and conclusions

- LentiGlobin BB305 gene therapy shows promising results in TDT
  - Patients with non-β^0/β^0 genotypes and ≥12 months follow-up remain free of RBC transfusions
  - Clinically meaningful reductions in transfusion volume and frequency in patients with β^0/β^0 genotypes
- Toxicity profile remains consistent with single-agent busulfan conditioning, with no evidence of clonal dominance
- LentiGlobin VCN strongly correlated with HbA^{T87Q} level at Month 6
- LentiGlobin manufacturing process using transduction enhancement for ongoing and planned clinical studies
  - Goal to increase drug product VCN and total hemoglobin production in all patients, regardless of genotype

HGB-204 study sites and investigators

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- Katherine Hammond
- Morris Kletzel

Children's Hospital of Philadelphia, UPenn
- Janet Kwiatkowski
- David Teachey
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- Marci Moriarty

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- Christina White
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