EHA 2017 Abstract S814

A Phase 3 Study to Evaluate Safety and Efficacy of LentiGlobin Gene Therapy for Transfusion-Dependent β-Thalassemia in Patients With a Non-β^0/β^0 genotype: The Northstar-2 (HGB-207) Trial

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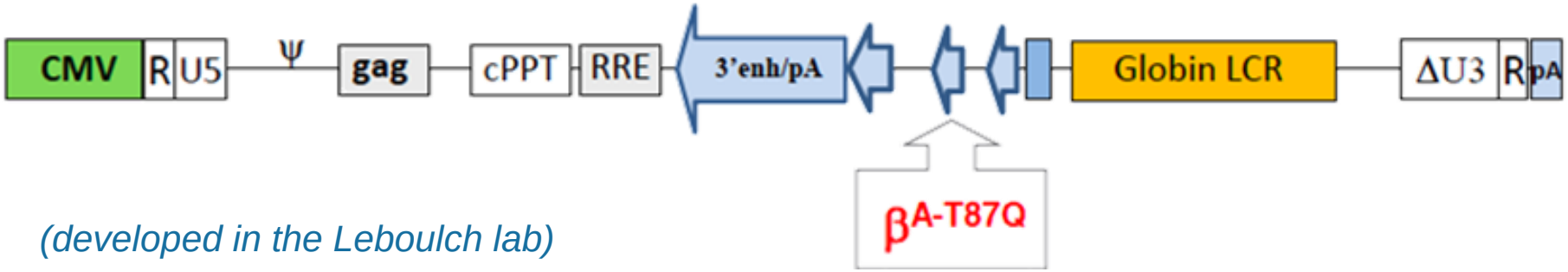
Gene therapy for transfusion-dependent β-thalassemia (TDT)

BB305 lentiviral vector



(developed in the Leboulch lab)

- Autologous gene therapy aims to correct TDT without GVHD/rejection risks of HSCT
- In Northstar (HGB-204) and HGB-205 phase 1/2 studies
  - LentiGlobin BB305 gene therapy eliminated transfusions in most patients with non-β^0/β^0 genotypes
  - Patients with β^0/β^0 genotypes (and ≥ 12 months follow up; n=5) had a median 63% reduction in transfusions
  - DP VCN in HGB-204 study (all patients) was **0.3 – 1.5** copies/cell
  - **<u>Key finding</u>: vector copy number (VCN) in drug product (DP) correlates with HbA^{T87Q}**
- **<u>Hypothesis</u>: higher VCN will generate HbA^{T87Q} in a therapeutic range without altering safety profile**

Northstar-2 (HGB-207) study of LentiGlobin BB305 gene therapy

- Investigating efficacy and safety of LentiGlobin BB305 in adolescents and adults with TDT and a non-$\beta^0\beta^0$ genotype
- Uses refined manufacturing process to yield higher DP VCNs
- **Primary endpoint:** proportion of patients who achieve **"transfusion independence"** (TI)
  - TI = maintain an average Hb ≥9 g/dL without RBC transfusions for ≥12 months

Current status of Northstar-2 (HGB-207) study

Key enrollment criteria

- 12 to 50 years of age
- Non-β^0/β^0 genotype
- 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

First patient infused December 2016

Target: 15 treated patients
(including ≥5 aged 12-17 years)

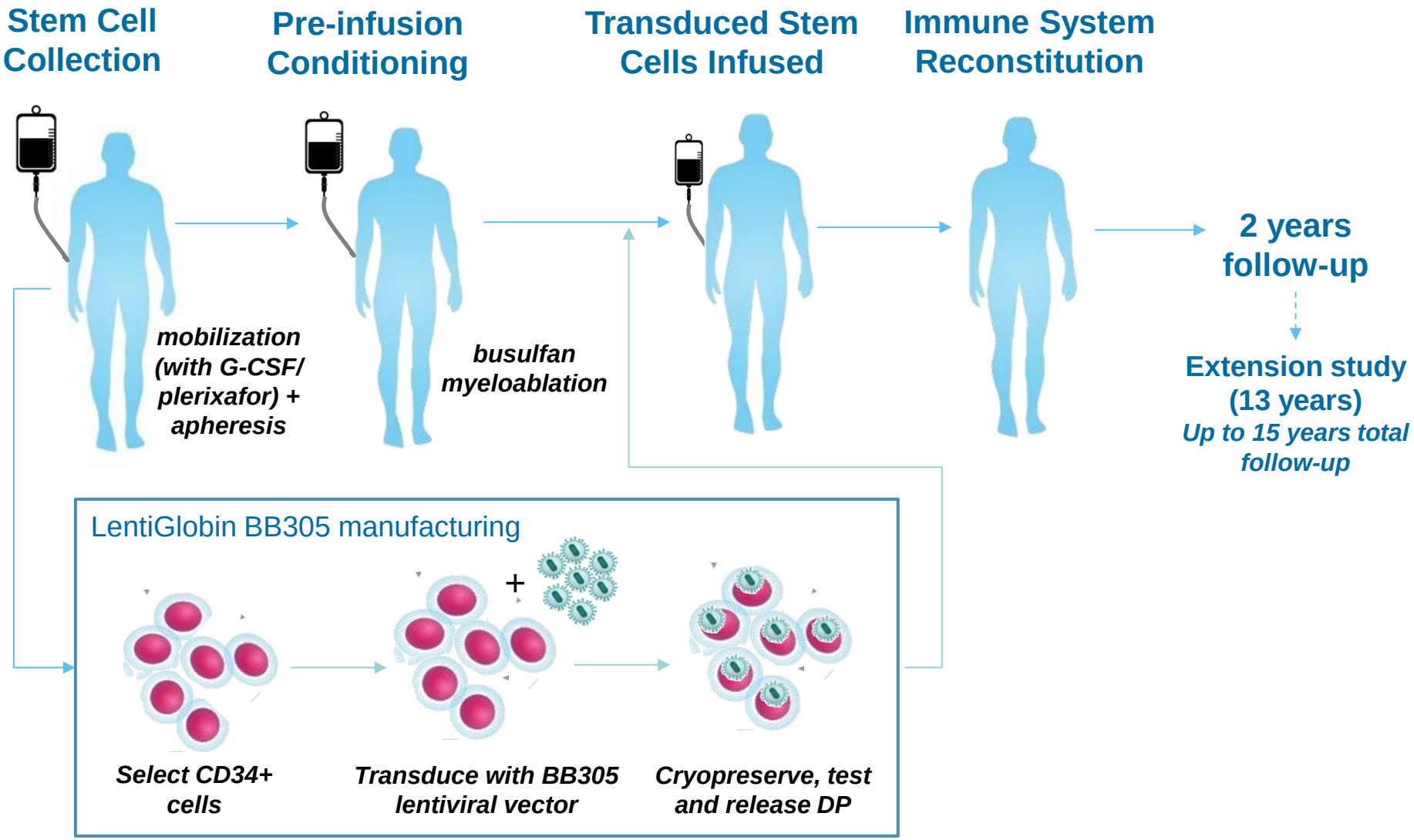
* Reasons for ineligibility: 2 withdrew consent, 2 screen failure due to liver biopsy findings

Numbers as of June 16, 2017

Overview of the Northstar-2 study process

Patient Treatment

Centralized Manufacturing



Patient characteristics

N=3 treated patients

Patient	1	2	3
Age (years)	20	20	22
Gender	F	F	F
Genotype	β^0/β^E	β^0/β^E	Homozygous IVS-I-5 (G>C)
Pre-Treatment pRBC Transfusions (mL/kg/year)	162.5	192.9	158.7
Liver Iron Concentration (mg/g) *(normal range <1.1 mg/g)*[1]	18.8	19.6	1.4
Cardiac T2* (msec) *(normal range >20 msec)*[2]	42.5	45.3	36.3
Splenectomy	N	N	Y

[1] Garbowski, M. W. et al (2014). Journal of Cardiovascular Magnetic Resonance, 16:40

[2] Carpenter, J. P et al (2011). Circulation, 123:1519-1528

Treatment-related parameters

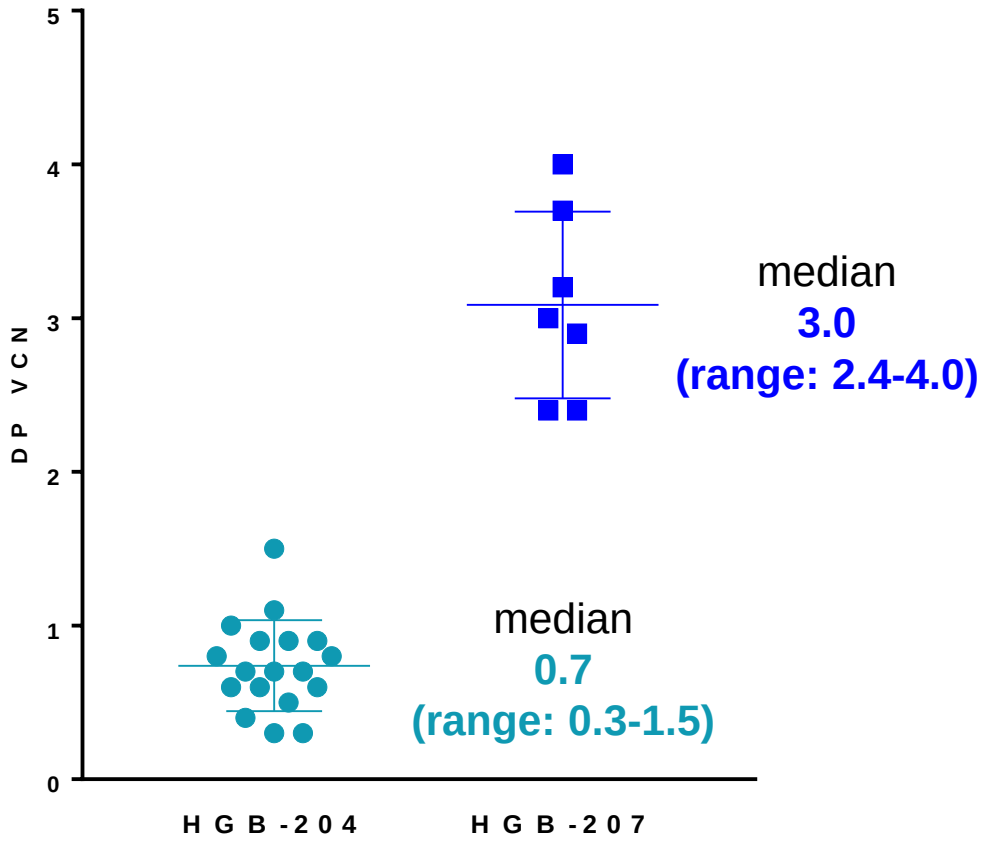
N=3 treated patients

Patient	1	2	3
VCN in drug product[1]	2.9	2.4	3.2, 2.4
Vector positive cells	77%	53%	77%, 82%
CD34+ cell dose (x10^6/kg)	7.0	13.6	8.1
Busulfan AUC (μM*min)[2]	4286	4337	4562
Neutrophil engraftment, study day[3]	25	24	19
Platelet engraftment, study day[4]	44	45	35
Follow up (months)	6	3	2

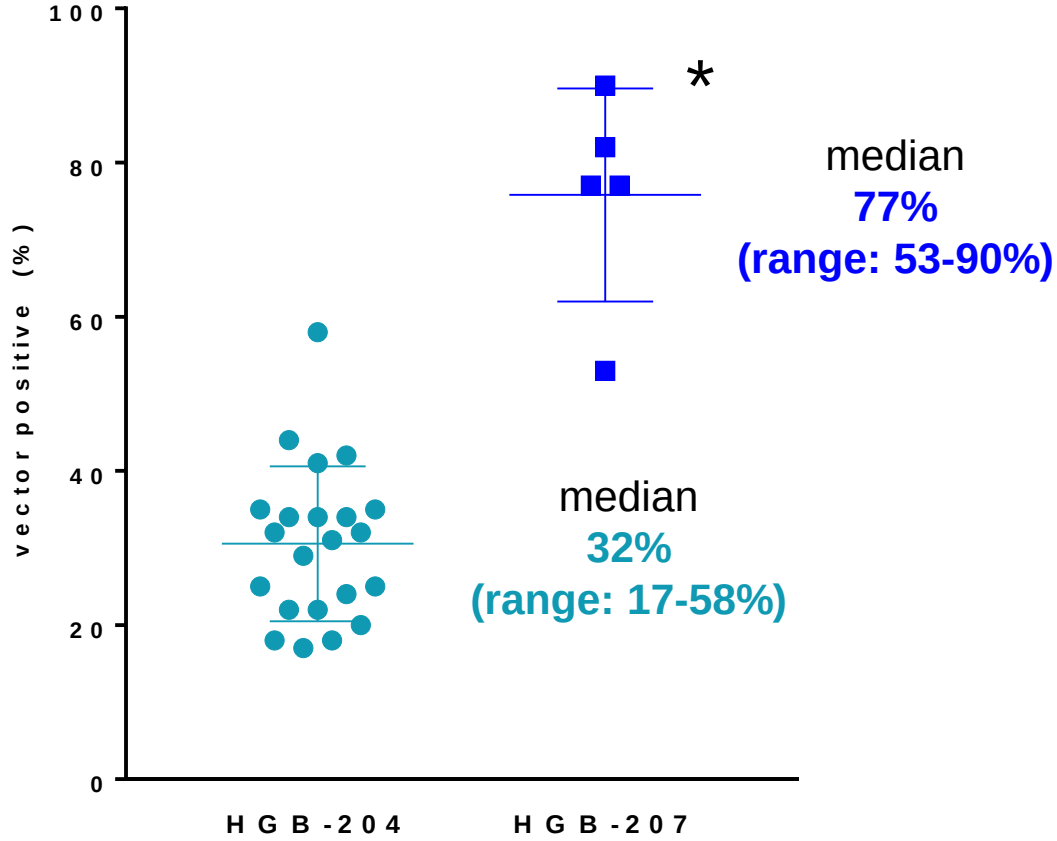
1. VCN: vector copy number (vector copies per diploid genome)
2. Estimated average daily busulfan exposure over four days
3. Absolute neutrophil count [AUC] ≥ 500 cells/μL for 3 consecutive days
4. Unsupported platelet count ≥ 20,000/μL

Refined manufacturing process yields higher drug product vector copy number and proportion of transduced cells

Vector copy number (VCN) in drug product



Proportion of CD34+ cells transduced



* Samples from EU manufacturing pending vector positive analysis

Initial safety summary (treatment emergent)

N=3 Infused patients

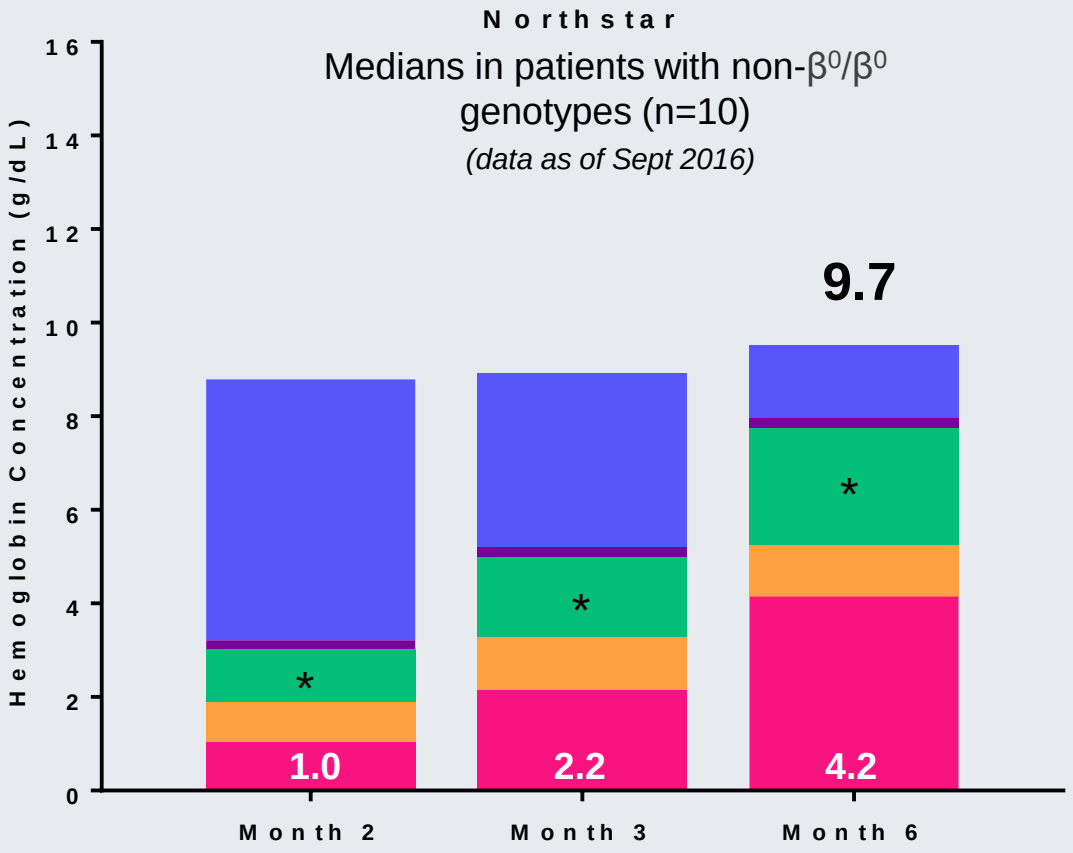
Patient	1	2	3
Follow up	**6 months**	**3 months**	**2 months**
Grade ≥3 non-hematologic adverse events [1, 2]	none	**Hypotension** (SAE; Grade 3) **Epistaxis** (Grade 3)	**Mucositis** (Grade 3)

- No significant veno-occlusive disease (VOD) of the liver or infections post-treatment
- No drug product-related AEs

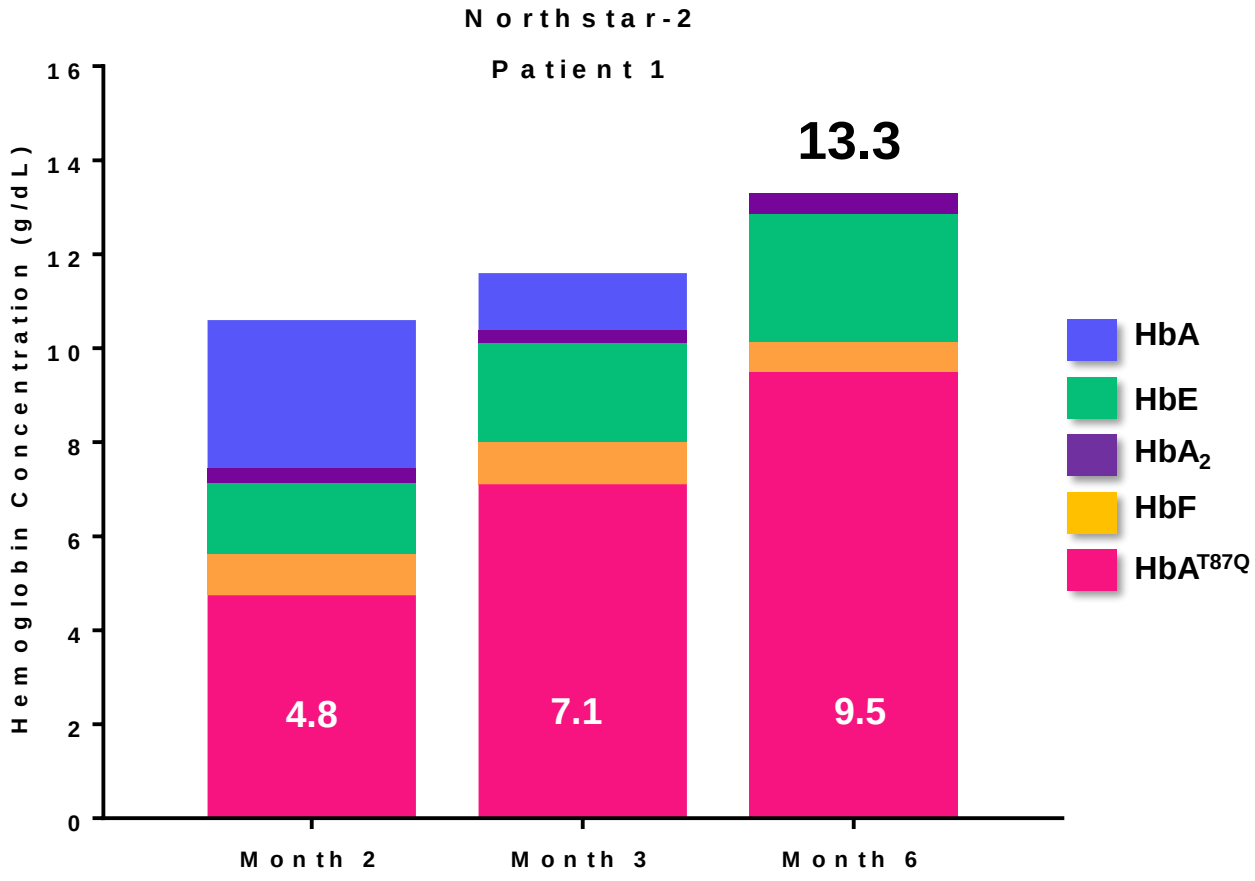
1. Hematological values typically decreased post-transplant are not shown
2. All AEs are reported from Day -8 to date of last contact (2-6 months)

First patient treated in Northstar-2 achieves normal total hemoglobin off transfusion

HGB-204



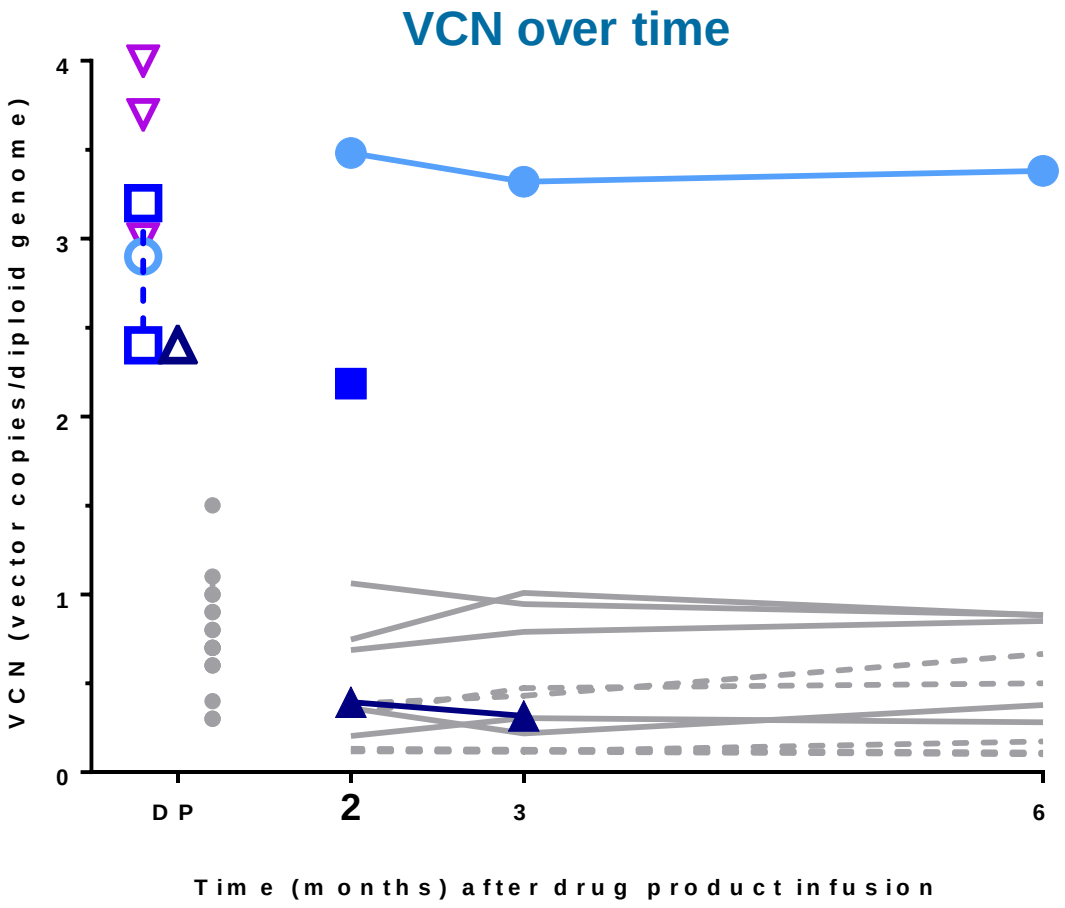
HGB-207

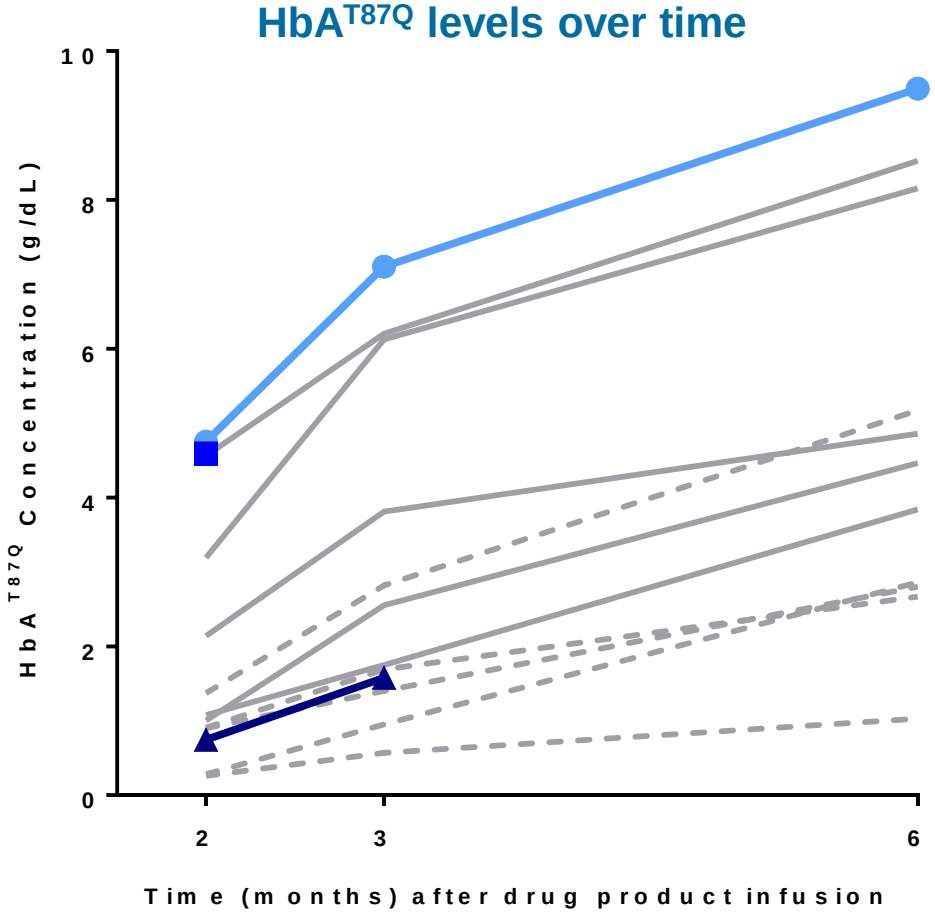


Last RBC transfusion: Day 33

* n=6 patients in Northstar study with HbE genotype

HbA^{T87Q} levels in Northstar-2 match or exceed HbA^{T87Q} in patients achieving early transfusion independence in Northstar





HGB-207

- Patient 1
- Patient 2
- Patient 3
- DP lots for patients pending transplant

HGB-204 (non-β^0/β^0 patients only**

- DP lots for treated patients
- Transfusion independent
- Not yet TI evaluable

*HGB-204 data as of ASH 2016

Northstar 3 (HGB-212)

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

- LentiGlobin gene therapy for TDT may eliminate RBC transfusions for many patients
- The refined manufacturing process in Northstar-2 yields higher DP VCNs
  - Initial results show equal or better *in vivo* VCN and HbA^{T87Q} production compared with the original Northstar study
  - A higher DP VCN may be sufficient for transfusion independence in most patients and mitigate patient-to-patient variability in HbA^{T87Q} production
- No LentiGlobin-related AEs reported with 2 to 6 months follow-up
  - AE profile of LentiGlobin still appears similar to autologous HSCT with myeloablative busulfan
  - Analysis of vector insertion patterns with higher DP VCN is pending

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