ASH 2018 Abstract #1025

LentiGlobin Gene Therapy for Patients with Transfusion-Dependent β-thalassemia (TDT): Results from the Phase 3 Northstar-2 and Northstar-3 Studies

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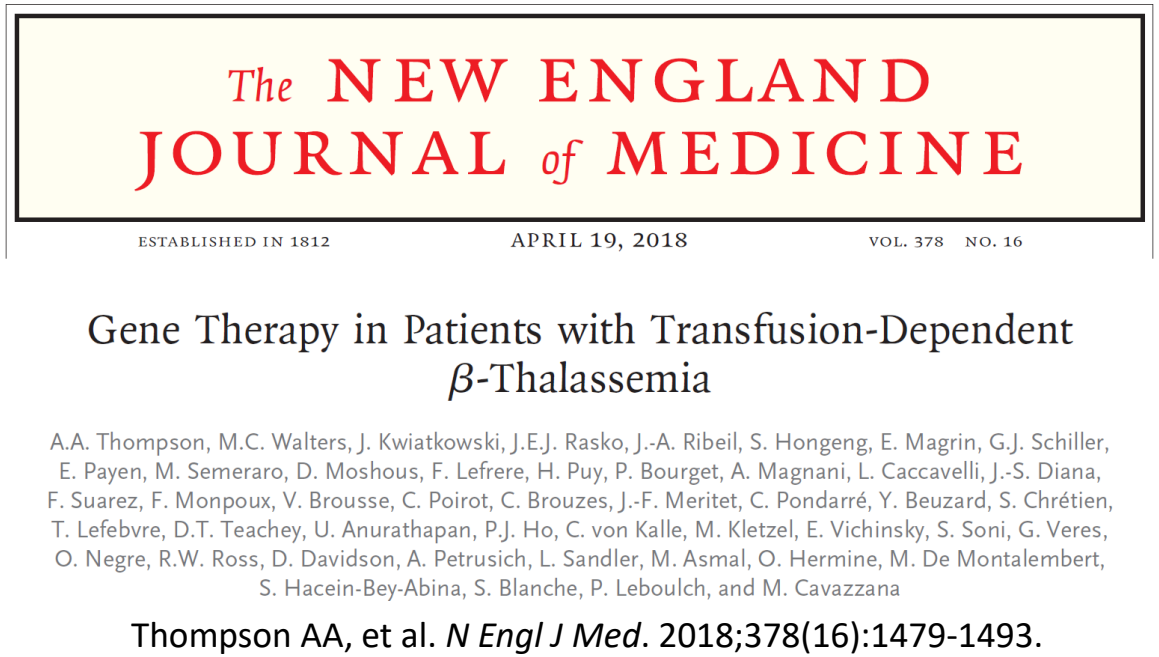
Studies of LentiGlobin gene therapy in adults and adolescents with transfusion-dependent β-thalassemia



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Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

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Thompson AA, et al. *N Engl J Med*. 2018;378(16):1479-1493.

- Patients achieved transfusion independence in the Phase 1/2 Northstar study[1]
  - 8/10 patients with non-β^0/β^0 genotypes
  - 3/8 patients with β^0/β^0 genotypes
- Drug Product VCN correlated with peripheral blood VCN which correlated to production of gene therapy-derived HbA^{T87Q}

- Refined manufacturing process is being evaluated in two phase 3 studies:
  - Northstar-2 (HGB-207): Patients with TDT and non-β^0/β^0 genotypes
  - Northstar-3 (HGB-212): Patients with TDT and β^0/β^0 genotypes*

1. Rasko JEJ, et al. ASH 2018. Abstract 167.

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

TDT, transfusion-dependent β-thalassemia; VCN, vector copy number

Northstar-2 (HGB-207): Phase 3 study in patients with TDT and non-β^0/β^0 genotypes

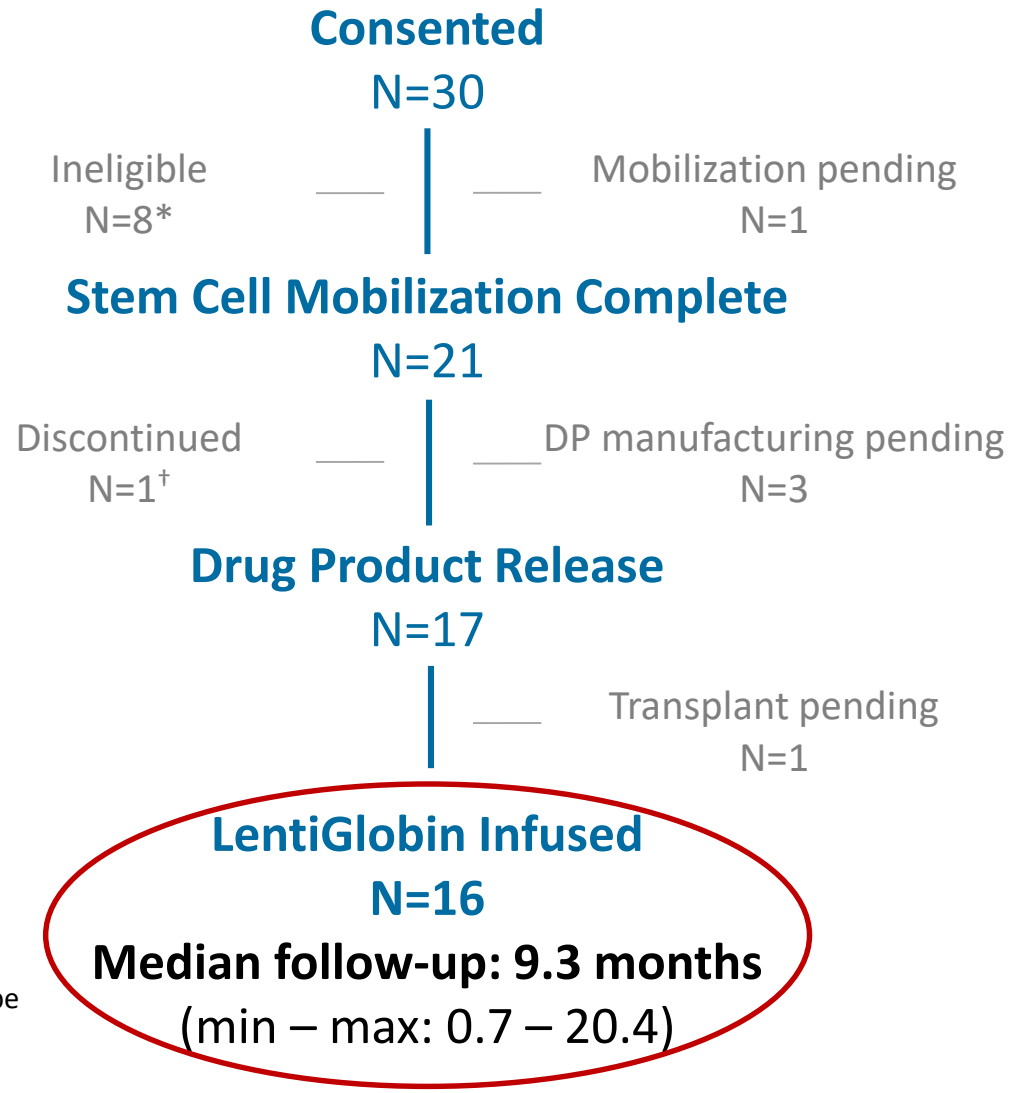
NORTHSTAR-2 STUDY

HGB-207

Phase 3, international, multi-center, open-label, single-arm

Target enrollment: **23 patients ≤ 50 years of age with TDT and non-β^0/β^0 genotypes**

Primary endpoint: Transfusion Independence
Weighted average Hb ≥ 9 g/dL without any transfusions for ≥ 12 months



*Reason for ineligibility: 3 withdrew consent, 4 screen failures due to advanced liver disease, 1 due to ineligible genotype
†Patient discontinued due to positive pregnancy test
Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia

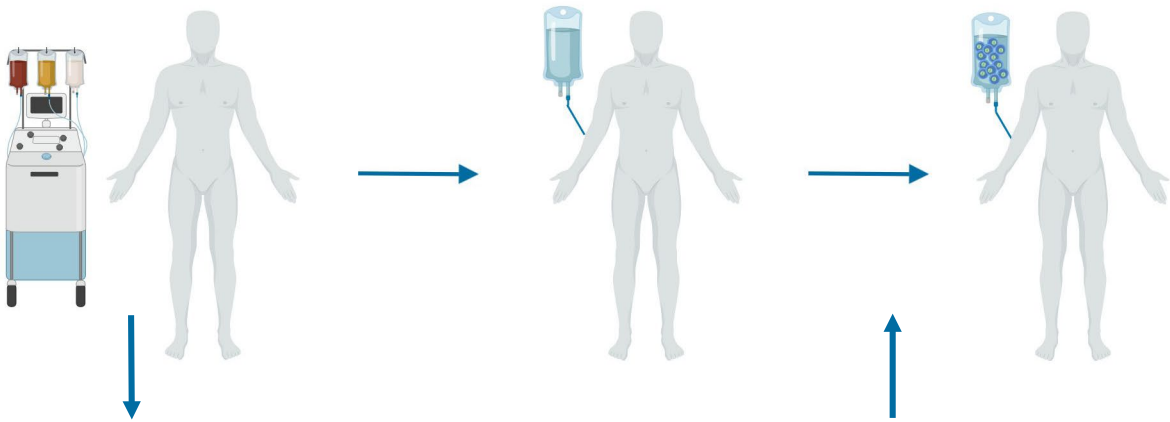
HGB-207: Study design

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

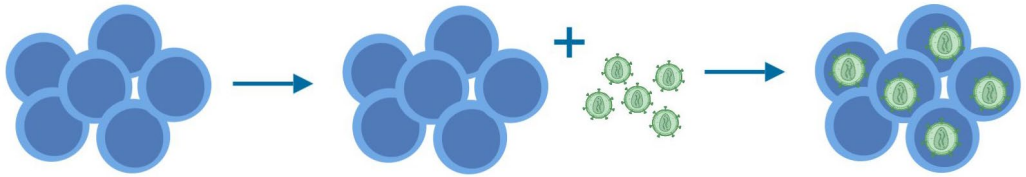
Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs



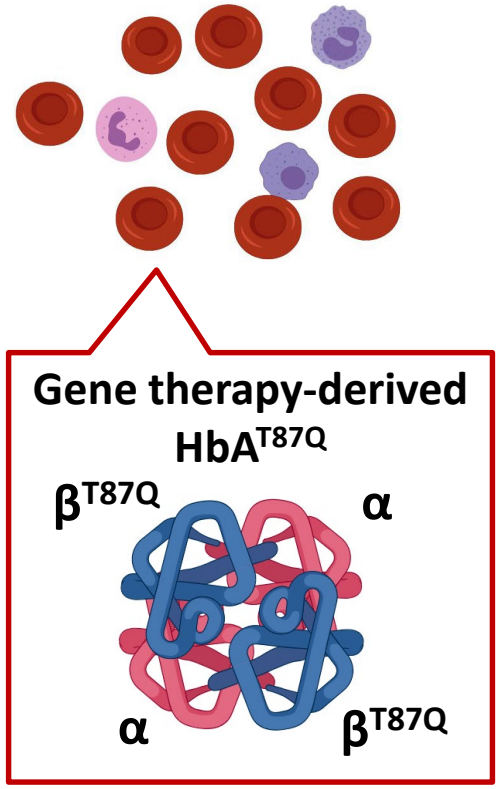
LentiGlobin DP centralized manufacturing



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-207: Patient and treatment characteristics

16 patients treated

Patient Characteristics		
Genotypes n, (%)	β^+/β^0 β^E/β^0 β^+/β^+	**7** (43.8) **6** (37.5) **3** (18.8)
Gender		**8 Males** **8 Females**
Age at consent median (min – max), years		**19** (8 – 34)
Pre-study pRBC transfusion volume annualized median (min – max), mL/kg/yr		**192.2** (152.3 – 274.4)
Liver iron concentration median (min – max), mg Fe/g dw		**6.4** (1.0 – 41.0)
Cardiac T2* median (min – max), msec		**36.5** (20.6 – 50.9)
Splenectomy n, %		**4** (25)

Drug Product Characteristics	
	median (min – max)
Drug product cell dose CD34+ cells x 10^6/kg	**7.7** (5.0 – 19.4)
Drug product VCN[†] vector copies/diploid genome	**3.1** (2.1 – 5.6)
CD34+ cells transduced[^] %	**81** (53 – 90)

Treatment Characteristics	
Busulfan AUC[‡] µM*min	**4545** (3709 – 8947)
Neutrophil engraftment[#] study day	**19** (13 – 32)
Platelet engraftment[§] study day	**44.5** (20 – 84)

[†]20 drug product lots manufactured for 16 patients; [^]19 drug product lots for 15 patients, one %LVV+ was not available at time of datacut; [‡]Estimated average daily busulfan exposure over 4 days; [#]N=15, 1 patient with 1 month of follow-up had not engrafted as of datacut, neutrophil engraftment defined as absolute neutrophil count ≥500 cells/µL for 3 consecutive days; [§]N=11, 4 patients with 1-2 months of follow-up had not engrafted as of datacut, platelet engraftment defined as 3 consecutive unsupported platelet counts ≥ 20,000/µL; AUC, area under the curve; pRBC, packed red blood cells; VCN, vector copy number

HGB-207: LentiGlobin safety profile remains consistent with myeloablative conditioning

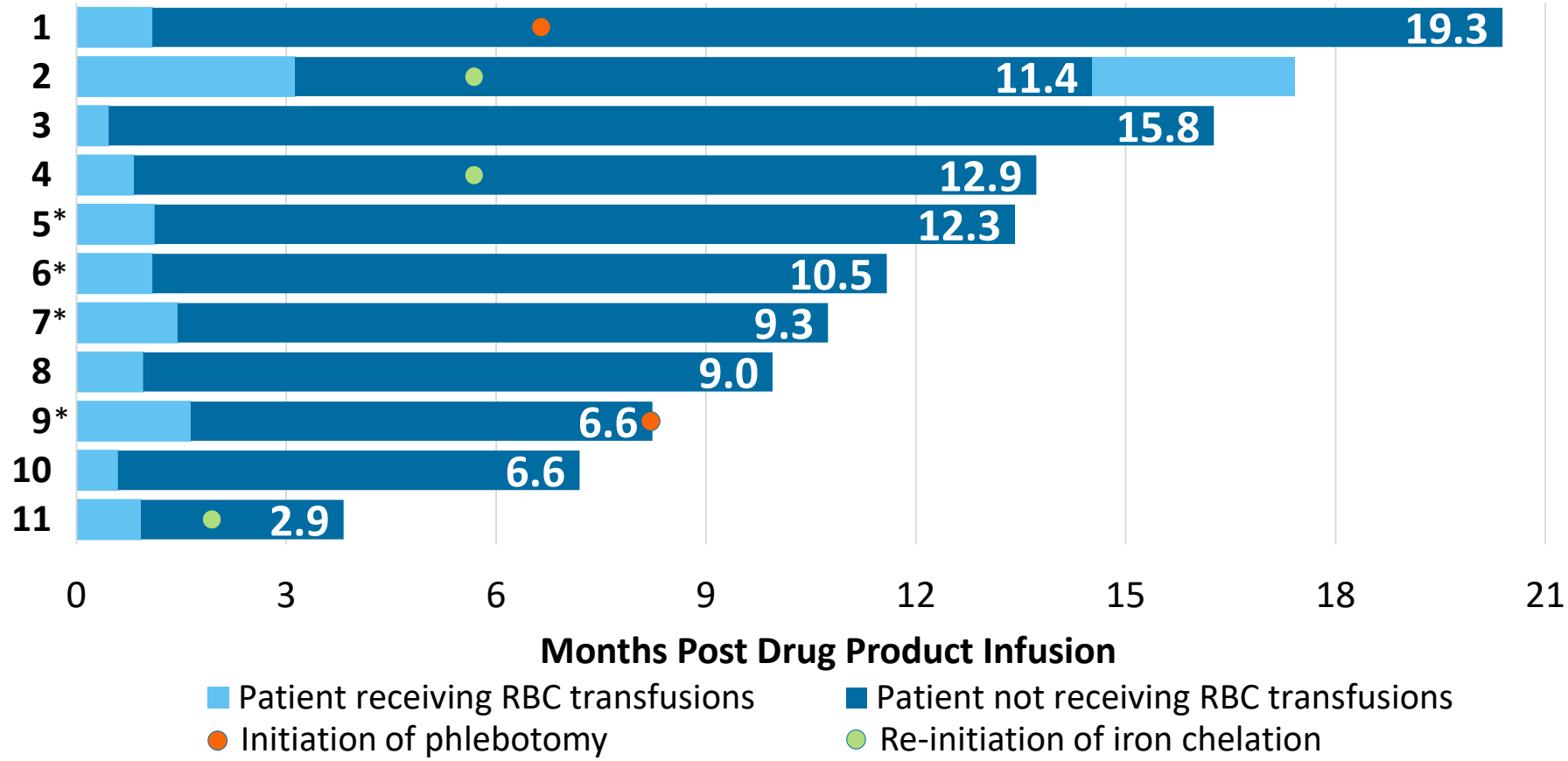
Non-hematologic grade ≥3 AEs* *Post LentiGlobin infusion in ≥2 patients*	**N = 16 n (%)**
Stomatitis	9 (56)
Febrile neutropenia	4 (25)
Epistaxis	3 (19)
Pyrexia	3 (19)
Veno-occlusive liver disease	3 (19)
ALT increased	2 (13)
Bilirubin increased	2 (13)
Hypoxia	2 (13)
Pharyngeal inflammation	2 (13)
Serious AEs* *Post LentiGlobin infusion in ≥1 patient*	
Veno-occlusive liver disease	3 (19)
Hypotension	1 (6)
Hypoxia	1 (6)
Lower respiratory tract infection	1 (6)
Pyrexia	1 (6)
Sepsis	1 (6)
Thrombocytopenia	1 (6)
Transfusion reaction	1 (6)

- No graft failure or deaths
- No vector-mediated replication competent lentivirus detected to date
- No early evidence of clonal dominance
- One grade 3 event of serious thrombocytopenia was considered possibly related to LentiGlobin
  - Patient had platelet counts of < 35 x10^9/L between platelet engraftment (Day +53) and last follow-up (Month 4)
- Three grade 4 VODs attributed to conditioning
  - One patient received VOD prophylaxis with ursodexoycholic acid
  - All were treated with defibrotide and events resolved

*Hematologic AEs commonly observed post-transplant have been excluded; AEs, adverse events; ALT, alanine aminotransferase; VOD, veno-occlusive liver disease

HGB-207: 10/11 patients are transfusion free with Hb > 11/dL

Time free from chronic transfusions in patients with ≥ 3 months follow-up

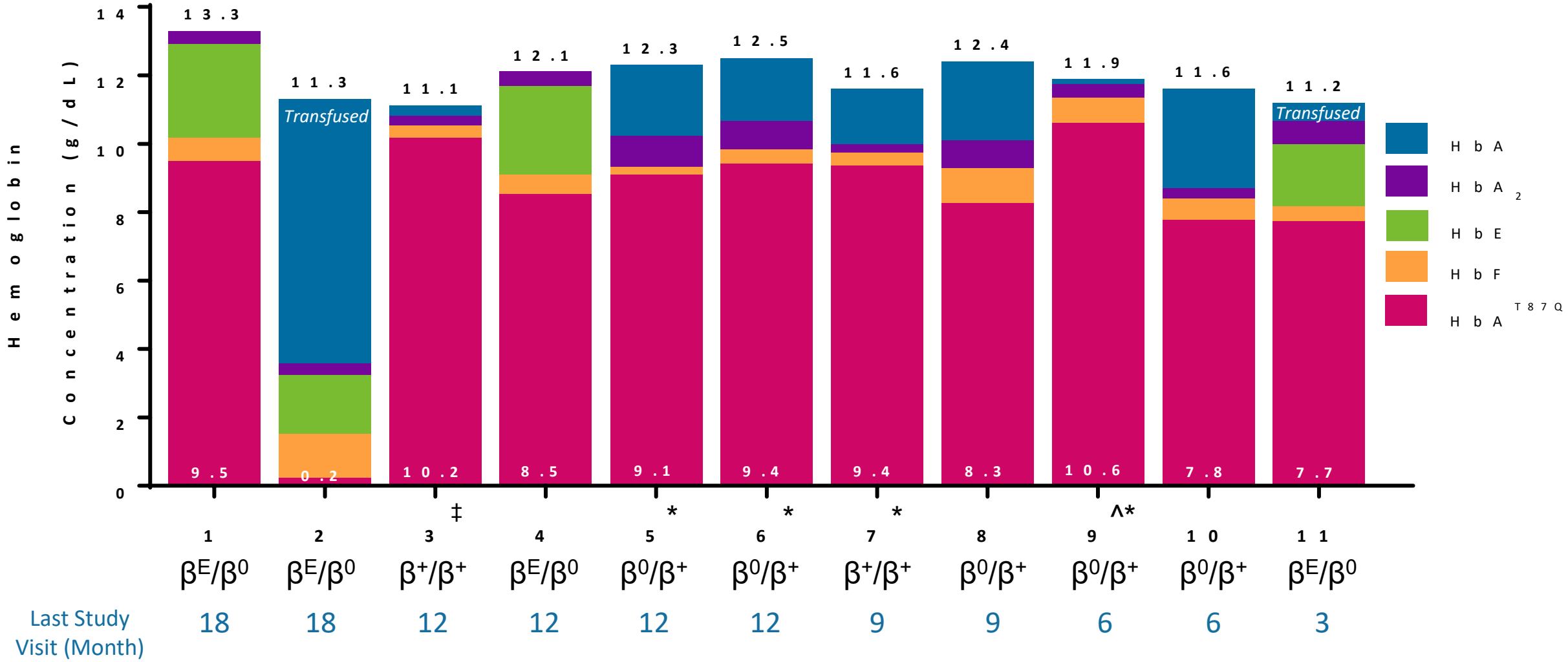


	Hb (g/dL) At last study visit	Peripheral VCN
1	13.3	3.2
2	11.3‡	0.4
3	11.1	2.2
4	12.1	1.7
5*	12.3	1.7
6*	12.5	2.9
7*	11.6	5.6
8	12.4	1.1
9*	11.9	4.9
10	11.6	5.4
11	11.2	5.6

Patients 1 and 3 have achieved the protocol definition of transfusion independence†

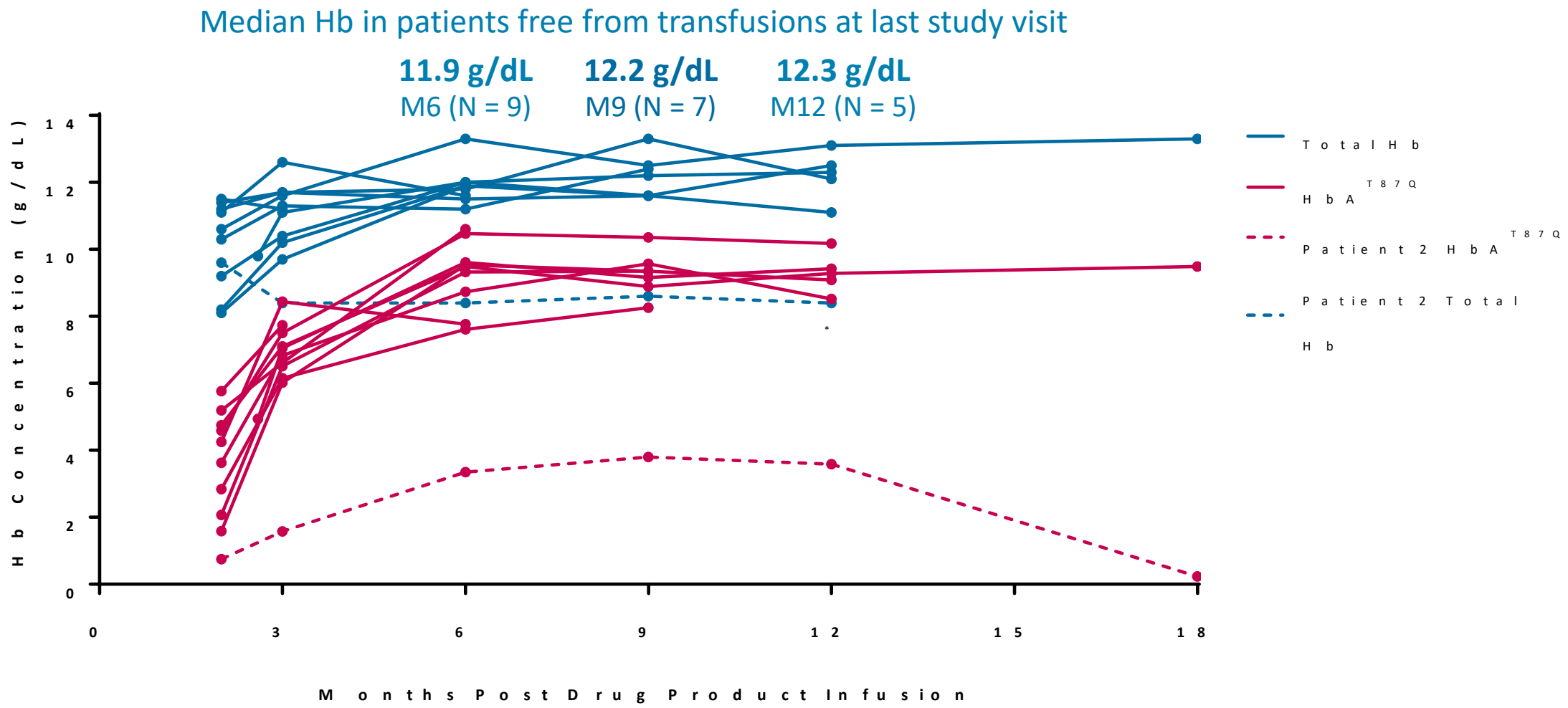
*Male patients; ‡Hb supported by transfusions; †Weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

HGB-207: Gene therapy-derived HbA^{T87Q} significantly contributes to total Hb in 10/11 patients



*Male patients; ‡Patient is homozygous for IVS-I-5 β-globin mutation; ^Patient is heterozygous for IVS-I-5 β-globin mutation. Hb, hemoglobin.

HGB-207: Stable transfusion-free total Hb and gene therapy-derived HbA^{T87Q}

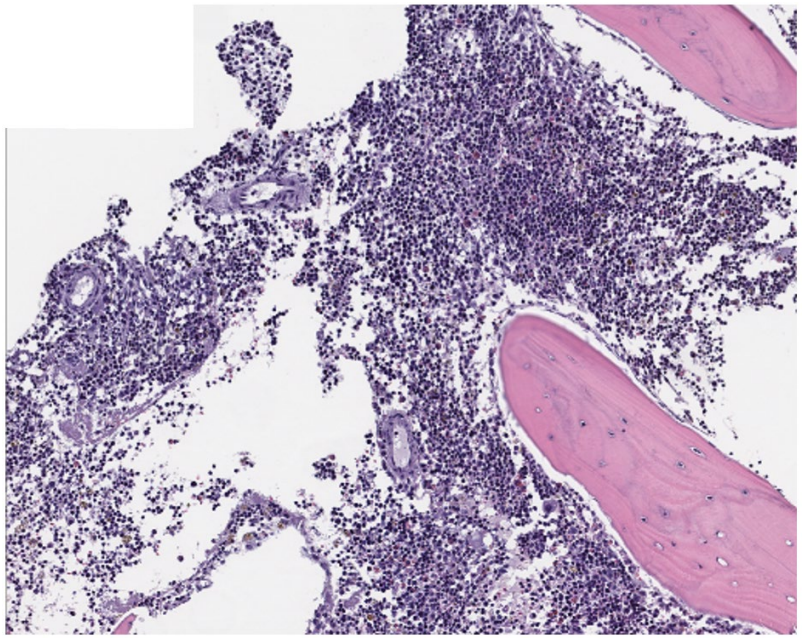


*Last Hb before patient restarted red blood cell transfusions; Hb, hemoglobin

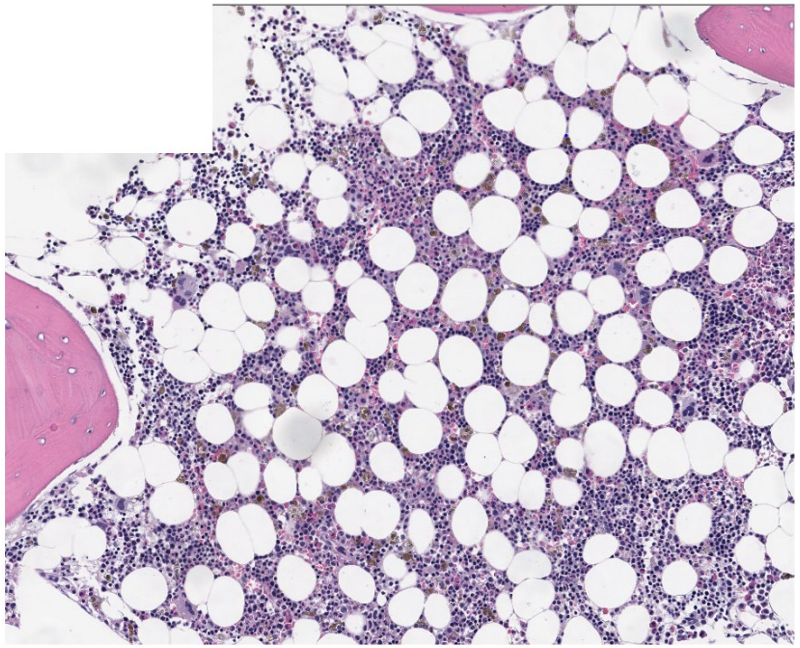
HGB-207: Improvement in erythropoiesis following LentiGlobin gene therapy

Patient 1 (20 yrs old) bone marrow analysis

Screening

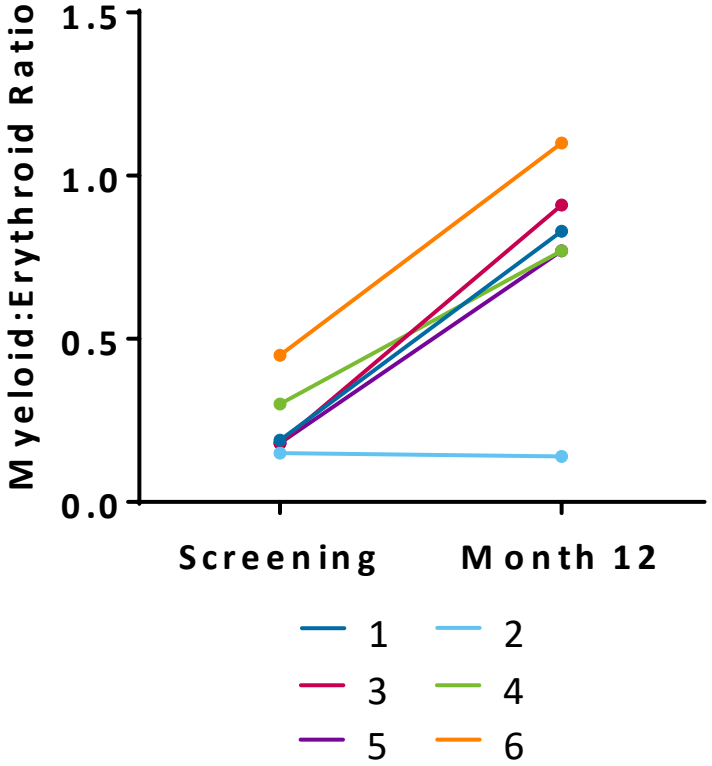


Month 12 post-LentiGlobin



Hb at Month 12: 13.1 g/dL

Myeloid:Erythroid ratio following LentiGlobin gene therapy



Normal M:E Ratio[1]: 3-4:1

1. Origa R. GeneReviews®. 2018.

Northstar-3 (HGB-212): Phase 3 study in patients with a β^0/β^0 genotype

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

NORTHSTAR-3 STUDY

HGB-212

Phase 3, international, multi-center, open-label, single-arm

Target enrollment: **~15 patients ≤ 50 years of age with TDT and a β^0/β^0 genotype***

Primary endpoint: **Transfusion Reduction**

≥ 60% reduction in transfused RBC volume 12 – 24 months post-DP infusion compared to the 24 months pre-DP infusion

Key secondary endpoint: **Transfusion Independence**

Weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months

Consented
N = 15

Ineligible
N = 1†

Mobilization pending
N = 4

Stem Cell Mobilization Complete
N = 10

DP manufacturing pending
N = 3

Drug Product Release
N = 7

Transplant pending
N = 4

LentiGlobin Infused
N = 3
Median follow-up: 4.2 months
(min – max: 1.4 – 9.2)

*Includes patients with the β^+ *HBB* mutation IVS-I-110 (G→A); †Reason for ineligibility liver iron content > 15 mg/g.
DP, drug product; RBC, red blood cell

Patient and treatment characteristics

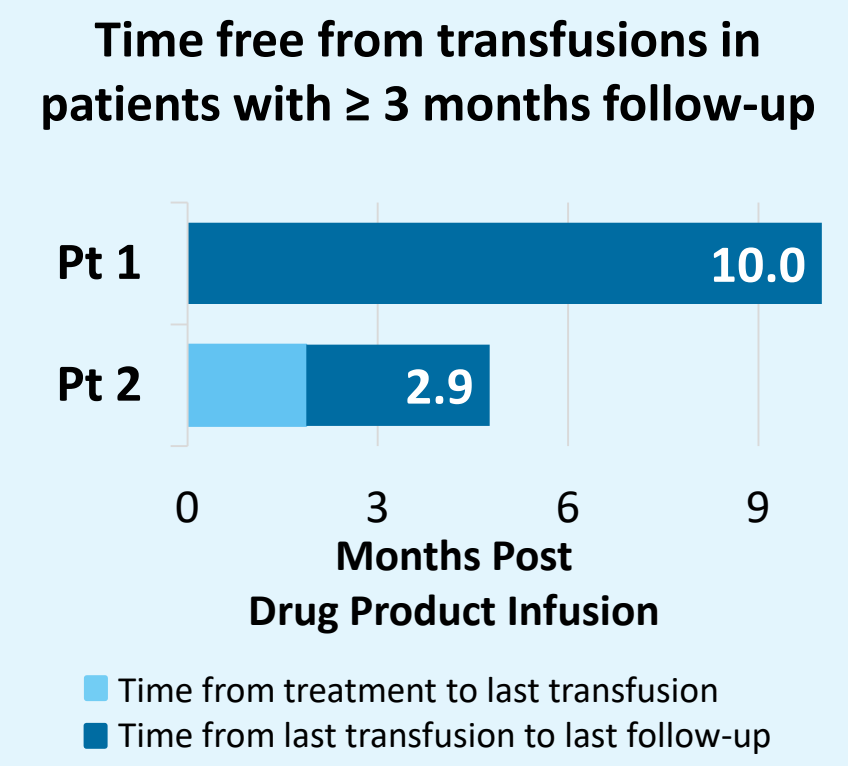
HGB-212

Patient Characteristics	N=3
Gender	**2 Males** **1 Female**
Genotype	Pt 1: **β^0/β^0** Pt 2: **β^0/β^+ (IVS-I-110)** Pt 3: **β^+/β^+ (IVS-I-110 homozygous)**
Age at consent yrs, median (min – max)	**17** (7 – 26)
Annualized pre-study pRBC transfusion volume mL/kg/yr, median (min – max)	**170.7** (160.2 – 189.9)
Splenectomy n, (%)	**1** (33%)

Drug Product Characteristics	N=3
Drug product cell dose CD34+ cells x10^6/kg, median (min – max)	**6.1** (5.9 – 12.9)
Drug product VCN* vector copies/diploid genome, median (min – max)	**3.3** (2.9 – 3.9)
CD34+ cells transduced* %, median (min – max)	**82** (78 – 85)
Treatment Characteristics	
Busulfan AUC† µM*min, median (min – max)	**5141** (4372 – 6351)
Neutrophil engraftment‡ study day, median (min – max)	**34** (14 – 38)
Platelet engraftment# study day, N=2^	**28, 50**

*5 drug products lots manufactured for 3 patients; †Estimated average daily busulfan exposure over 4 days; ‡Absolute neutrophil count ≥500 cells/µL for 3 consecutive days; #Three consecutive unsupported platelet counts ≥ 20,000/µL; ^ Patient 3 had not achieved platelet engraftment as of September 14, 2018 however had a platelet count of 61,000/µL at last study visit as reported by the investigator as of November 19, 2018, not from programmed statistical outputs
AUC, area under the curve; DP, drug product; pRBC, packed red blood cells; VCN, vector copy number

Preliminary outcomes of patients treated in HGB-212

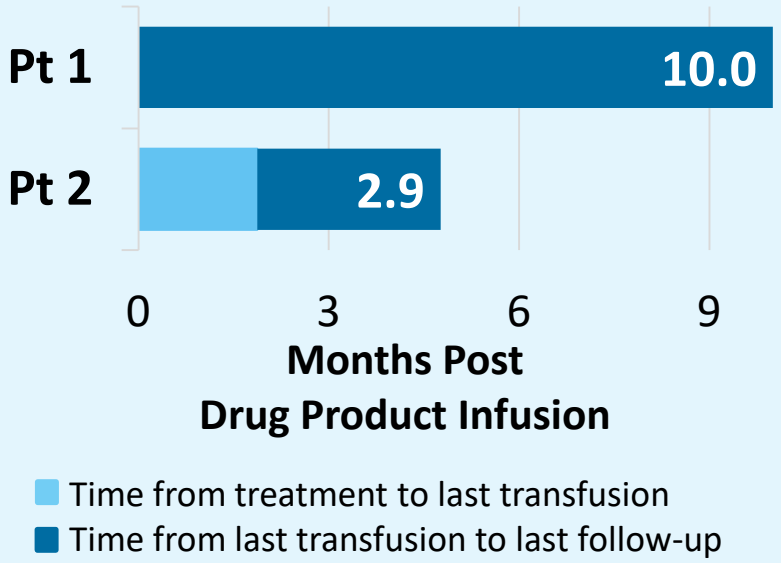


AEs, adverse events; DP, drug product; Hb, hemoglobin; RBC, red blood cell; VCN, vector copy number (vector copies/diploid genome)

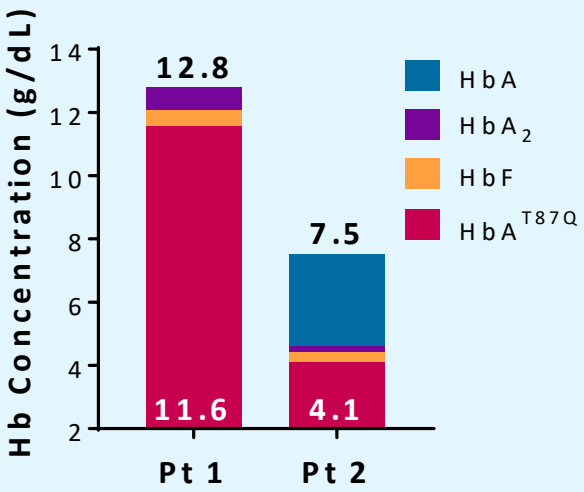
Data as of September 14, 2018 unless otherwise noted

Preliminary outcomes of patients treated in HGB-212

Time free from transfusions in patients with ≥ 3 months follow-up



Hb fractions in patients with ≥ 3 months follow-up



	Pt 1	Pt 2
Peripheral VCN	3.4	2.2
Study Visit	M9	M3

Data as of September 14, 2018 unless otherwise noted

AEs, adverse events; DP, drug product; Hb, hemoglobin; RBC, red blood cell; VCN, vector copy number (vector copies/diploid genome)

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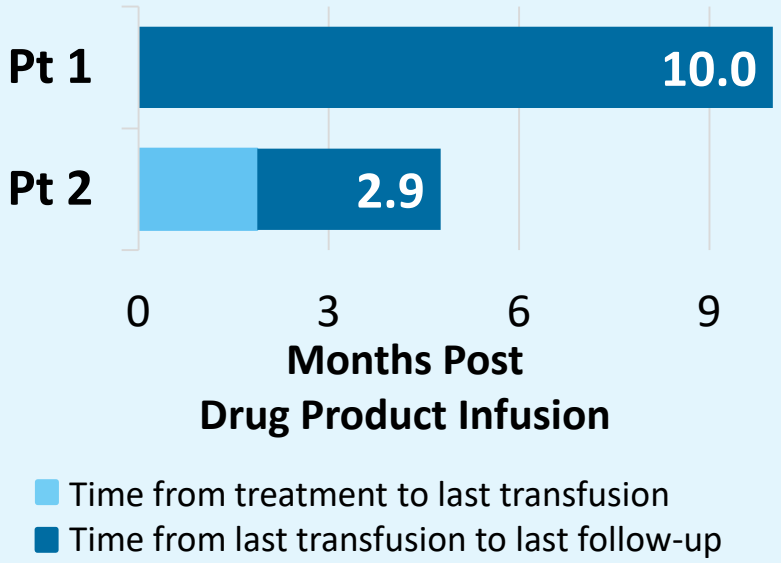

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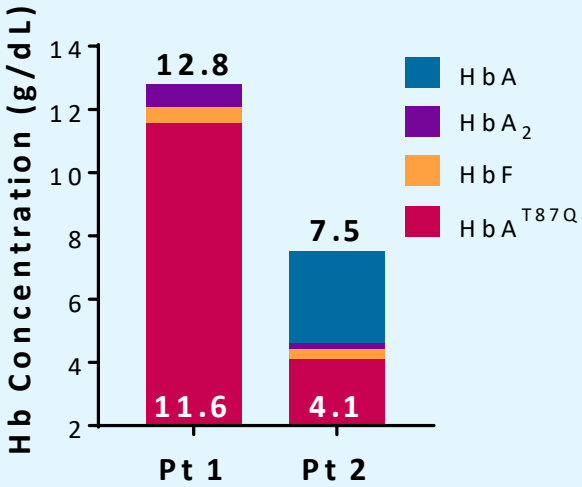


	Pt 1	Pt 2
Peripheral VCN	3.4	2.2
Study Visit	M9	M3

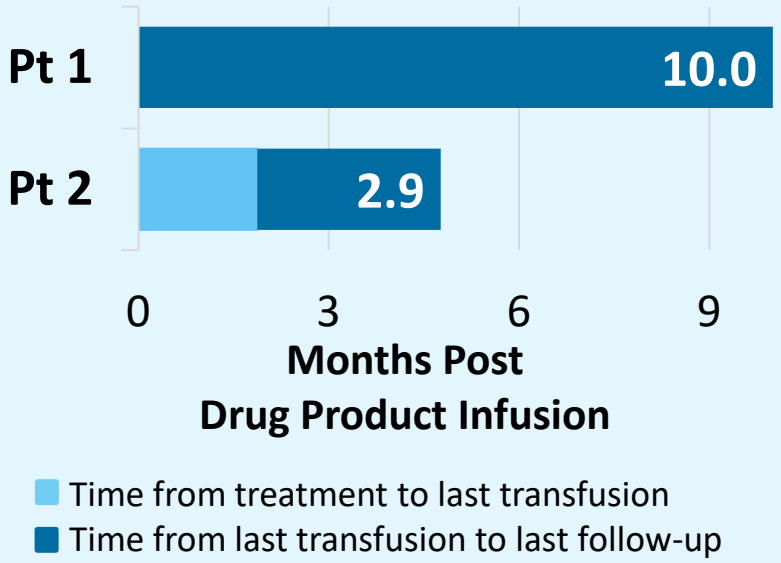
Investigator-reported Hb at last visit*

	Hb (g/dL)	Last RBC transfusion
Pt 1 26 yr old male β^0/β^0	**13.8** M12	M0
Pt 2 7 yr old female β^0/β^+ (IVS-I-110)	**10.1** M6	M1.9
Pt 3 17 yr old male β^+/β^+ IVS-I-110 homozygous	**11.6** M3	M1.4

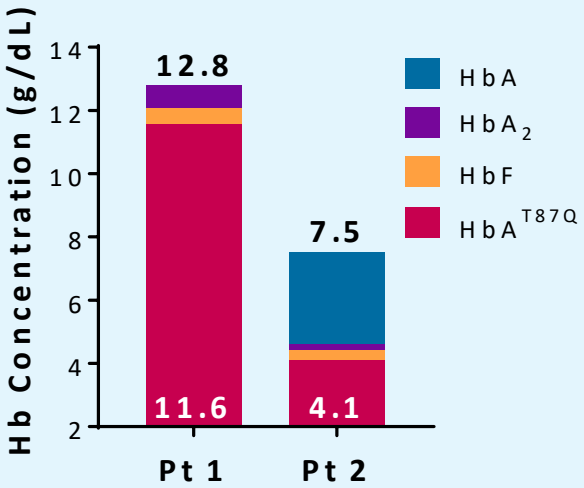
*Includes investigator reported data as of November 19, 2018, not from programmed statistical outputs;
AEs, adverse events; DP, drug product; Hb, hemoglobin; RBC, red blood cell; VCN, vector copy number (vector copies/diploid genome)

Preliminary outcomes of patients treated in HGB-212

Time free from transfusions in patients with ≥ 3 months follow-up



Hb fractions in patients with ≥ 3 months follow-up



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Pt 3 17 yr old male β^+/β^+ IVS-I-110 homozygous	**11.6** M3	M1.4

- Non-hematologic† grade ≥3 AEs following DP infusion in the 3 patients treated included*:
  - Stomatitis (67%) and one event each of anal inflammation, epistaxis, febrile neutropenia, pharyngeal inflammation
- No serious AEs or DP-related AEs were reported following LentiGlobin infusion*

*Includes investigator reported data as of November 19, 2018, not from programmed statistical outputs; †Hematologic AEs commonly observed post-transplant have been excluded

AEs, adverse events; DP, drug product; Hb, hemoglobin; RBC, red blood cell; VCN, vector copy number (vector copies/diploid genome)

Data as of September 14, 2018 unless otherwise noted

Summary

- 10/11 adults and adolescents with transfusion dependent β-thalassemia and non-β^0/β^0 genotypes with ≥ 3 months follow-up in Northstar-2 have stopped chronic transfusions
  - Total Hb of 11.1 – 13.3 g/dL consisting of 7.7 – 10.6 g/dL gene therapy-derived Hb, HbA^{T87Q}, at last visit
  - Bone marrow morphology indicates improvements in erythropoiesis
- Manufacturing refinements have translated into robust and stable *in vivo* HbA^{T87Q} production
- Hb > 10 g/dL reported in both patients with a β^0/β^0 genotype or β^+ *HBB* IVS-I-110 mutation and ≥ 6 months follow-up in the Northstar-3 study
- The safety profile of LentiGlobin gene therapy remains generally consistent with myeloablative busulfan conditioning, including serious AEs of vaso-occlusive liver disease
  - One episode of grade 3 thrombocytopenia was considered possibly related to LentiGlobin
- MAA under review by EMA for the treatment of adults and adolescents with TDT and a non-β^0/β^0 genotype

AE, adverse event; EMA, European Medicines Agency; Hb, hemoglobin; MAA, marketing authorization application; TDT, transfusion-dependent β-thalassemia

Thank you to the study participants and their families

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