LentiGlobin Gene Therapy in Patients with Sickle Cell Disease: Updated Interim Results from HGB-206

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HGB-206: Study of LentiGlobin gene therapy for severe sickle cell disease (SCD)

HGB-206

Key Enrollment Criteria

- 18+ years of age
- History of symptomatic SCD
- Adequate organ function
- No previous HSCT or gene therapy

Study Objectives

- Primary objective: Safety
- Key secondary objectives:
  - Frequency of VOCs and ACS
  - HbA^{T87Q} production, Hb, Hb fractions
  - Vector copy number in peripheral blood

Target enrollment: up to 29

Study initiated August 2014

ACS, acute chest syndrome; Hb, hemoglobin; HSCT, hematopoietic stem cell transplant; VOC, vaso-occlusive crisis

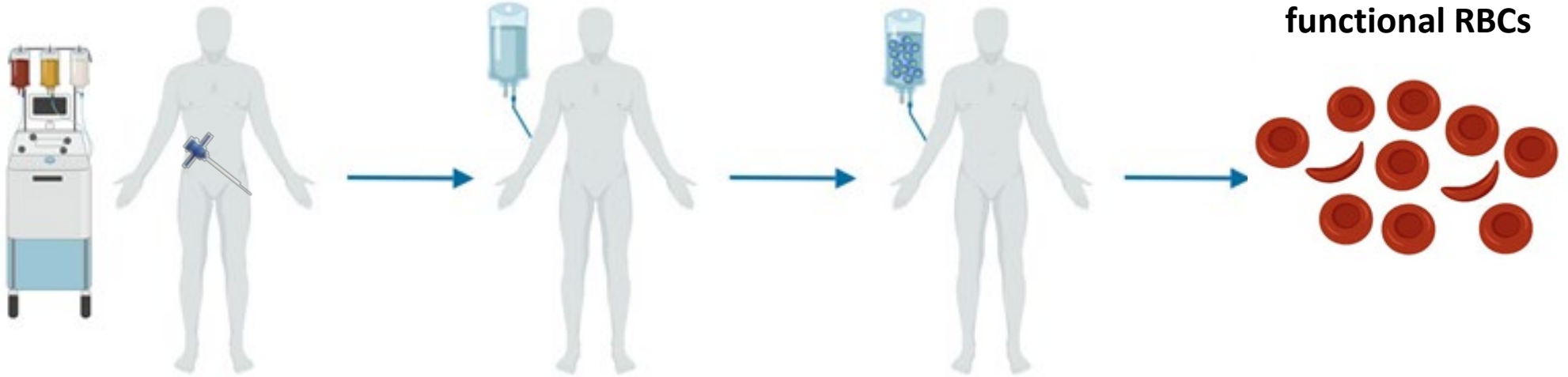
HGB-206: LentiGlobin gene therapy overview in patients with SCD

HSC collection
Bone marrow harvest or mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs



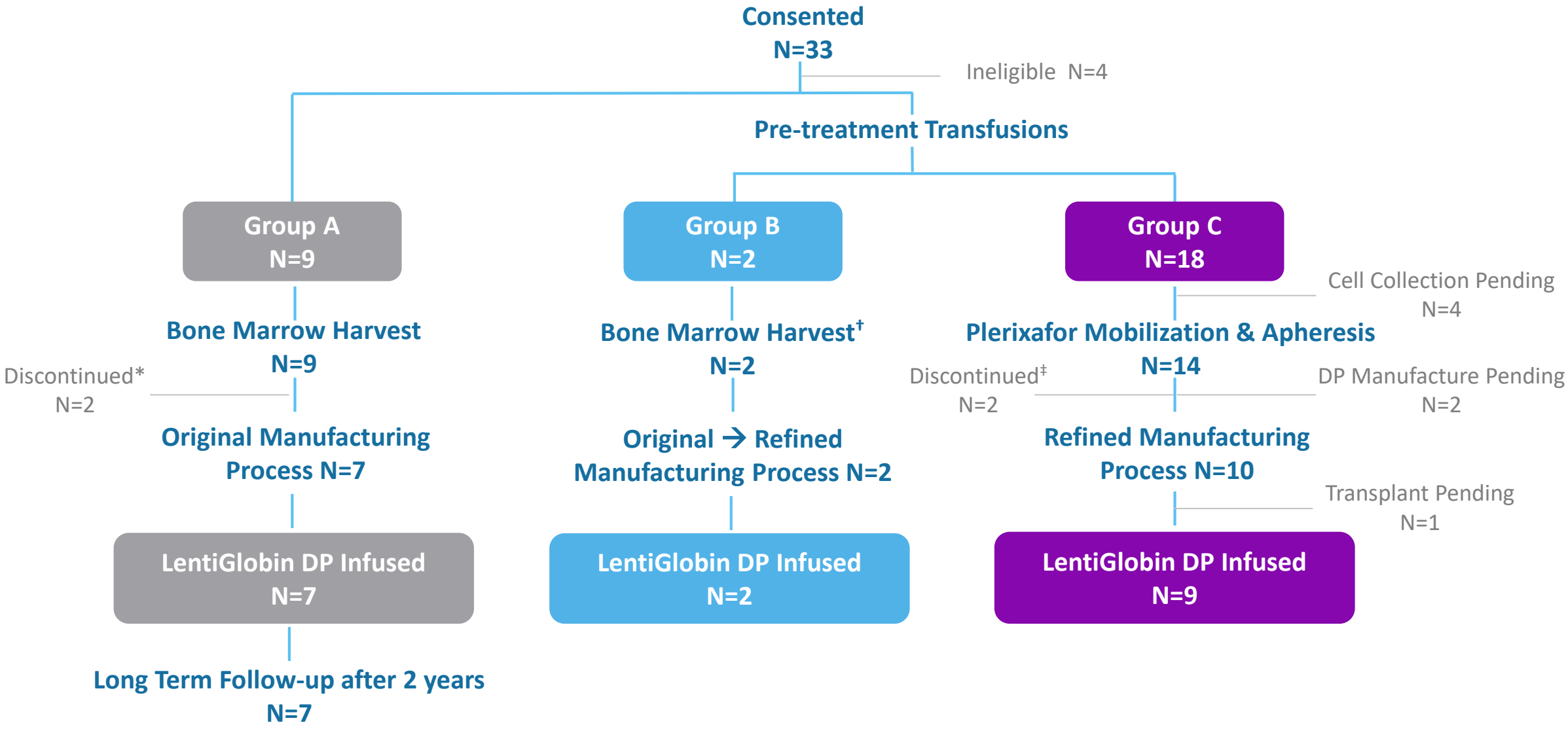
2-yr follow-up

Long-Term Follow-Up Study

	Group A	Group B	Group C
Pre-collection transfusion regimen	Optional	Required	Required
HSC source	Bone marrow	Bone marrow	Mobilized PB
Manufacturing process	Original	Orig → Refined	Refined

DP, drug product; HSC, hematopoietic stem cell; PB, peripheral blood; RBCs, red blood cells

HGB-206: Study disposition



*1 due to insufficient cell collection, 1 withdrew consent; †1 patient also received a single mobilization cycle to collect cells for back-up; ‡1 due to adverse event, 1 withdrew consent

HGB-206: Patient characteristics

N=25 patients who started cell collection

Parameter	Group A N=9	Group B N=2	Group C N=14
Age at consent, years median (min – max)	**26** (18 – 43)	**24.5** (22 – 27)	**25.5** (18 – 36)
Gender	**2 F 7 M**	**0 F 2 M**	**6 F 8 M**
Genotype, β^S/β^S	**9**	**2**	**14**
SCD History			
Hydroxyurea, n	**5**	**2**	**8**
VOCs[*], n Annualized no. of events, median (min – max)	**7** **4.5** (2.0 – 27.5)	**2** **10.0** (2.5 – 17.5)	**9** **6.5** (3.5 – 14.0)
ACS[†], n Annualized no. of events, median (min – max)	**1** **1**	**1** **1**	**2** **1** (1 – 1)
Stroke, n	**2**	**0**	**3**
TRJV >2.5 m/s, n	**1**	**0**	**0**

*≥2 events/year in preceding 2 years; [†]≥2 episodes in preceding 2 years, with ≥1 episode in the past year or in the year prior to the initiation of regular transfusions

ACS, acute chest syndrome; F, female; M, male; TRJV, tricuspid regurgitant jet velocity; VOC, vaso-occlusive crisis

HGB-206: Treatment characteristics

N=18 infused patients

Parameter	Group A N=7 Median (min – max)	Group B N=2 (Pt 1312, Pt 1313)	Group C N=9 Median (min – max)
Follow-up, months	**29.9** (29.2 – 38.9)	**14.3, 17.2**	**5.2** (0.5 – 9.2)
No. of bone marrow harvests	**2** (1 – 4)	**2, 3**	N/A
No. of mobilization cycles	N/A	1†	**2** (1 – 3)
No. of apheresis procedures per mobilization cycle	N/A	1	**1** (1 – 2)
CD34+ cells collected per collection cycle, x10^6 cells/kg	**4.0** (0.1 – 10.8)	**6.3‡, 1.2‡**	**9.2** (5.6 – 21.6)
Average busulfan AUC, µM*min (over 4 days)	**4747** (4084 – 5290)#	**5256, 5017**	**4787** (4608 – 5182)
Neutrophil engraftment, days (ANC ≥ 500 /µl)	**22** (17 – 29)	**23, 28**	**19.5** (18 – 24)§
Platelet engraftment, days (platelets > 50k /µl)	**56** (29 – 63)	**31, 61**	**28** (19 – 136)^

†For research purposes; ‡Median per BMH; #Based on data for 6 patients; §Based on data for 8 patients; ^Based on data for 7 patients

- 6/7 Group C patients had platelet engraftment by Day 90

HGB-206: Favorable safety profile with plerixafor mobilization/apheresis vs bone marrow harvest (BMH)

In 26 BMHs in 11 patients, 18 Grade ≥ 3 AEs were reported in 6 patients*

Patients with Grade ≥ 3 AEs within 7 days of BMH	n (%) N=11
Procedural pain[1]	6 (54)
Anemia	2 (18)
Vaso-occlusive pain[2]	2 (18)
Lymphocyte count increased	1 (9)

[1]Considered serious in 2 patients; [2]3 events in 2 patients, all considered serious

In 35 apheresis procedures in 14 Group C patients†, 5 Grade ≥ 3 AEs were reported in 3 patients

Patients with Grade ≥ 3 AEs within 7 days of 1st plerixafor in a mobilization cycle	n (%) N=14
Vaso-occlusive pain[1]	2 (14)
Abdominal pain	1 (7)
Hypomagnesemia	1 (7)
Non-cardiac chest pain	1 (7)

[1]Were considered serious and consistent with patients' histories of VOEs

*Patient could have experienced same AE more than once; †Plerixafor mobilization/apheresis for research purposes was performed in 1 Group B patient, resulting in 3 Grade 3 AEs: vaso-occlusive pain, increased AST and increased ALT

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; VOE, vaso-occlusive event

HGB-206: Safety profile consistent with myeloablative busulfan conditioning

Non-hematologic Grade ≥ 3 AEs* *Post DP infusion in ≥ 2 patients*	n (%) N=18
Stomatitis	13 (72)
Febrile neutropenia	11 (61)
Vaso-occlusive pain	5 (28)
Pharyngeal inflammation	4 (22)
Bacteremia	2 (11)
Dyspnea	2 (11)
Epistaxis	2 (11)
Non-cardiac chest pain	2 (11)
Pyrexia	2 (11)

*Hematologic AEs commonly observed post-transplant have been excluded

- No cases of VOD
- No VOEs post DP infusion in Group C patients
- No graft failure, deaths or vector-mediated RCL
- No evidence of clonal dominance observed to date
- Serious AEs were reported in 12 patients, vaso-occlusive pain was most common (n=5; 4 in Group A & 1 in Group B)
  - **1 Grade 4 SAE of myelodysplastic syndrome (MDS) in Group A patient**

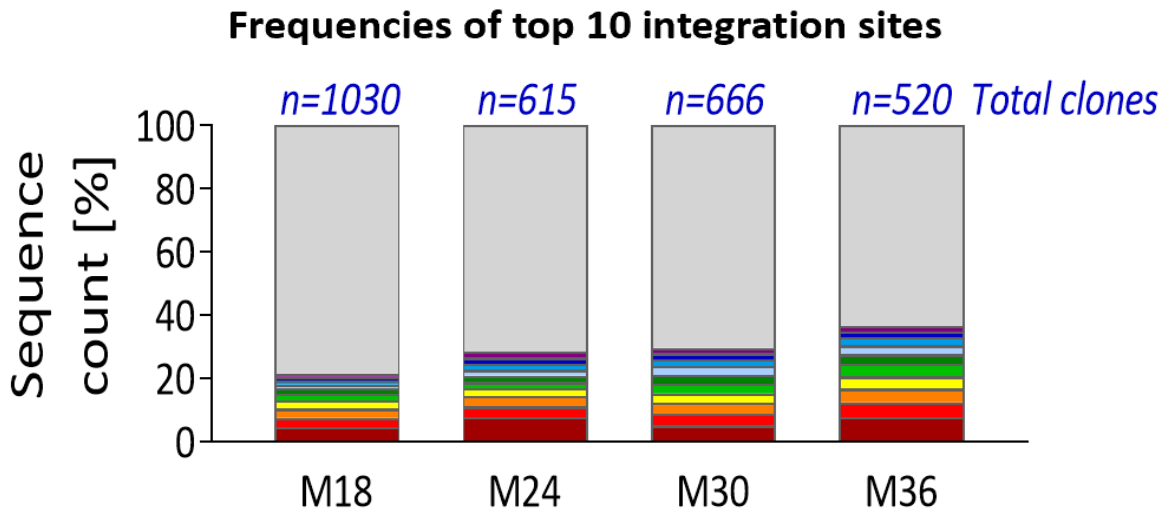
AE, adverse event; DP, drug product; RCL, replication competent lentivirus; SAE, serious adverse event; VOD, veno-occlusive liver disease; VOE, vaso-occlusive event

HGB-206: A case of myelodysplastic syndrome with excess blasts in a patient >40 years old

- **Grade 4 SAE of MDS in a Group A patient ~36 months post LentiGlobin infusion**
- **BM biopsy showed 15% myeloblasts/dysplasia with monosomy 7 and 19p abnormality in 8/20 metaphases**

No evidence of clonal dominance (No IS > 30%)

- Largest 5 clones varied over 18 months



Blast cells (CD34+) had low VCN consistent with no lentiviral vector (LVV) genotoxicity

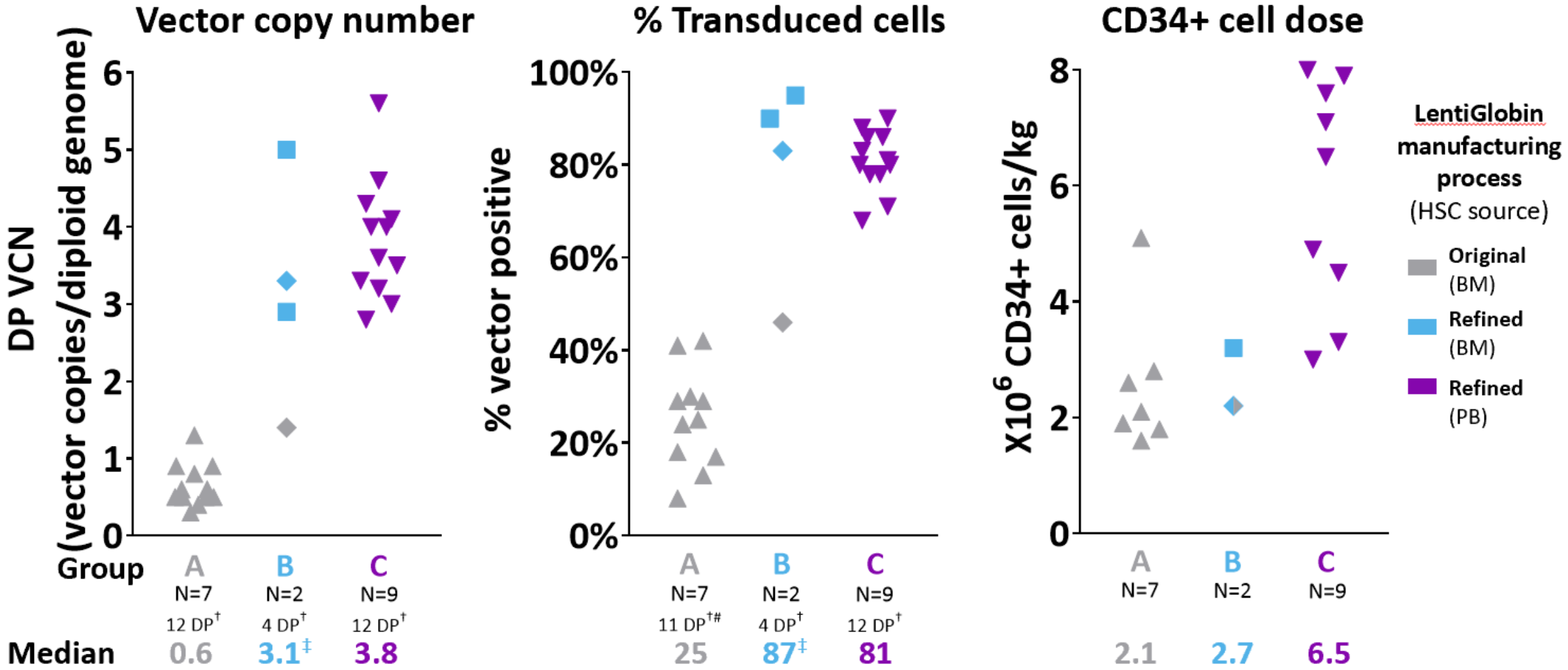
Marrow cell populations after MDS diagnosis	Purity (%)	VCN (c/dg)
Unsorted	N/A	0.14
CD34-	98	0.21
CD34+ blasts	93	0.02

- Given LVV genotoxicity would cause VCN > 1 in CD34+ blasts, MDS SAE is considered unlikely related to LentiGlobin GT*
- MDS is a risk of autologous HSCT with alkylating agents such as busulfan[1-3]

*Per safety database; BM, bone marrow; c/dg, copies/diploid genome; GT, gene therapy; HSCT, hematopoietic stem cell transplant; IS, integration site; MDS, myelodysplastic syndrome; N/A, not applicable; VCN, vector copy number

1. Rege KP et al., BMT 1998; 2. Howe R et al., BMT 2003; 3. McNerney ME et al., Nat Rev Cancer 2017

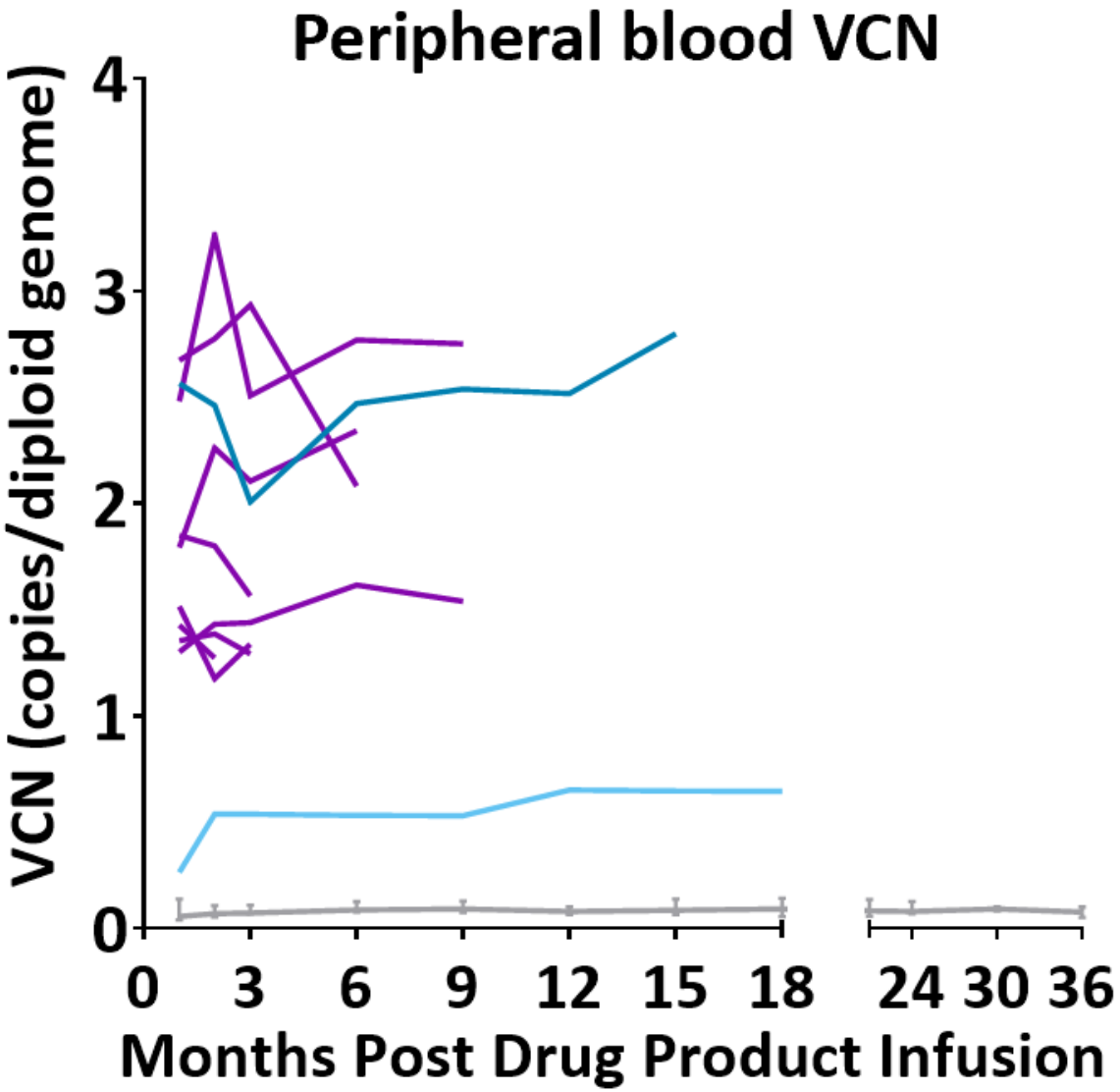
HGB-206: Refinements to manufacturing and cell harvest improved drug product characteristics

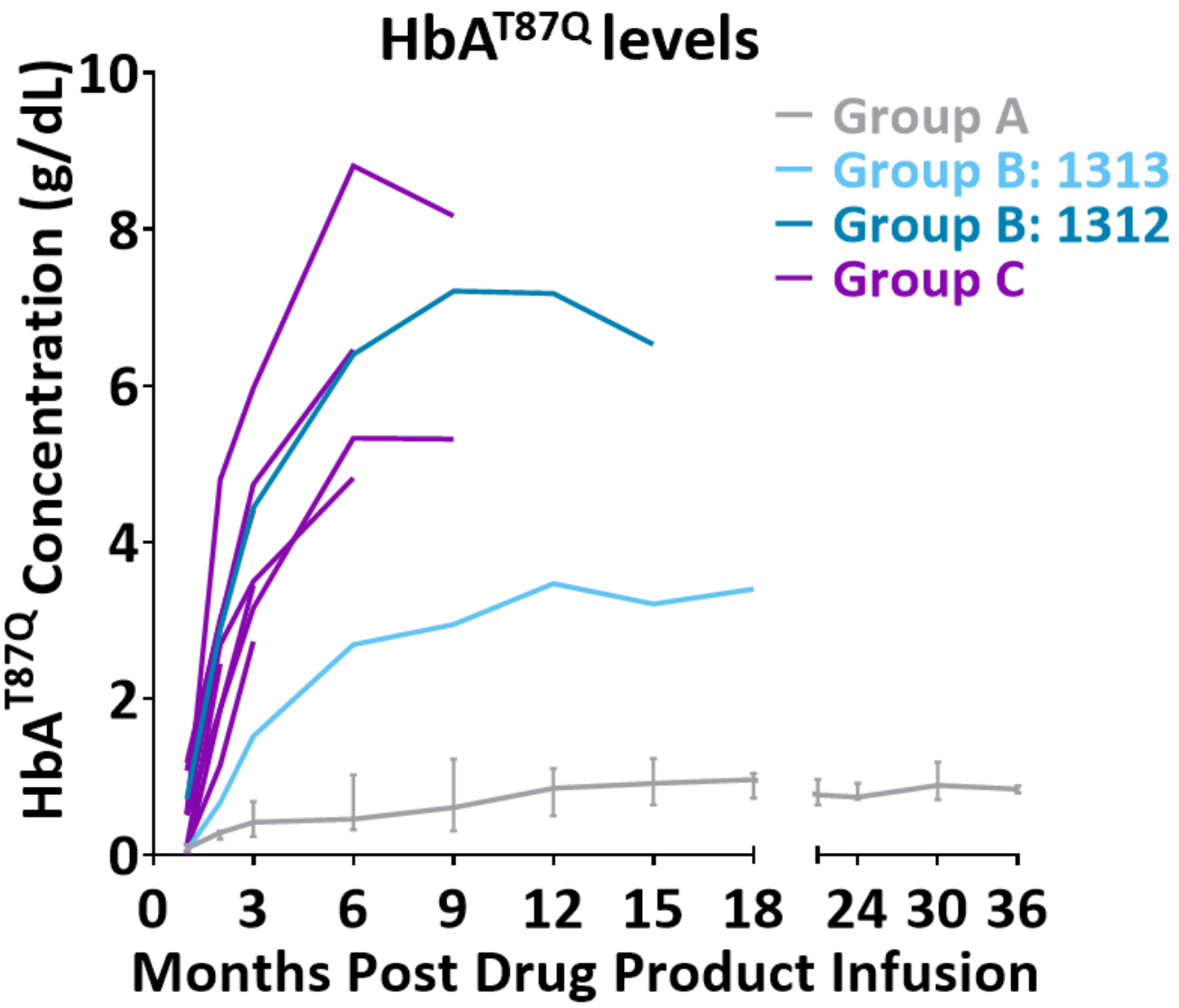


†Number of DP exceeds number of patients since some patients were harvested or mobilized more than once; # % Transduced cells not available for 1 DP at time of analyses; ‡1 Group B DP lot was made using original manufacturing process, while the other 3 DP lots were made using refined manufacturing process

BM, bone marrow; DP, drug product; HSC, hematopoietic stem cell; PB, peripheral blood; VCN, vector copy number

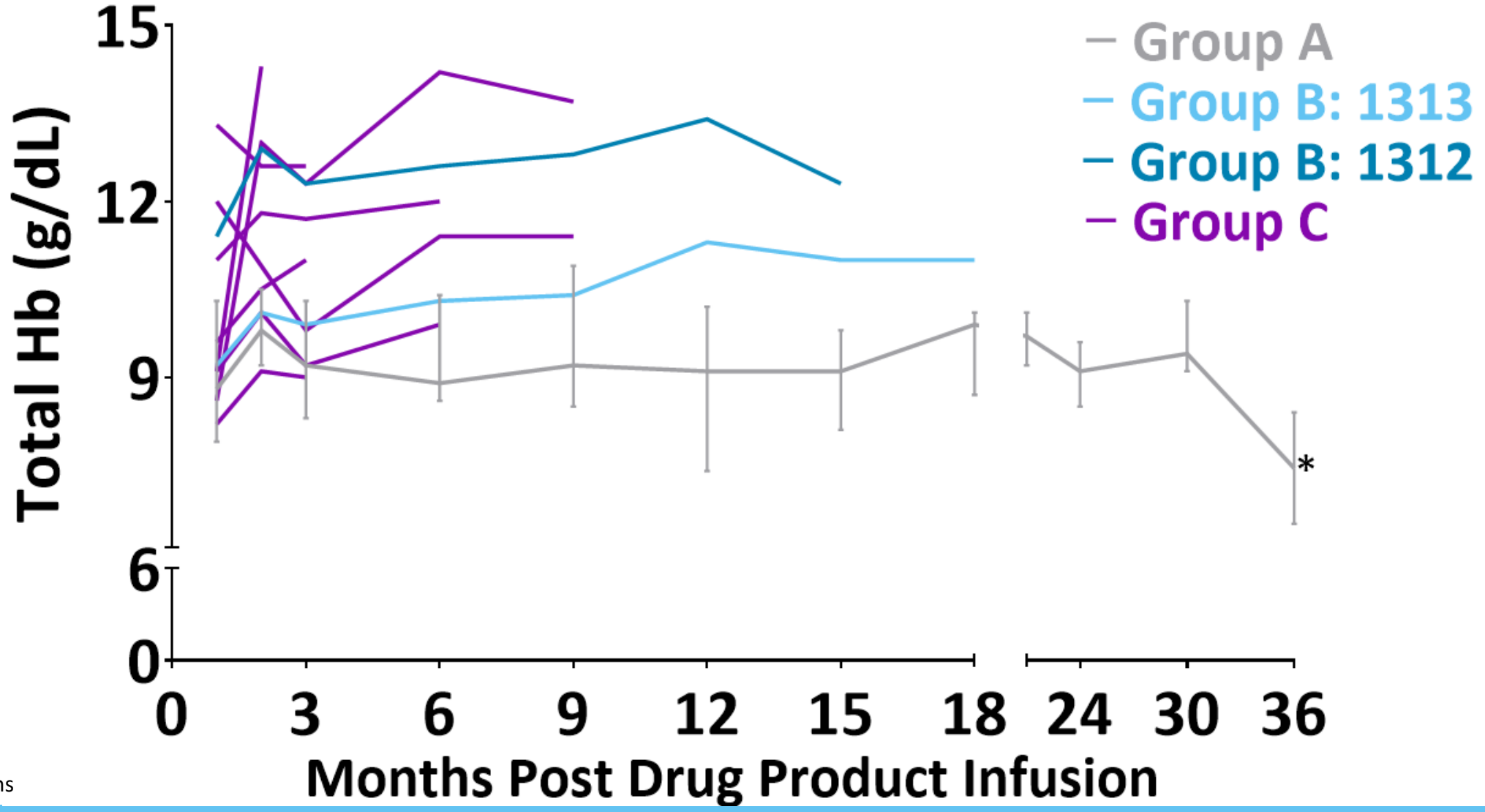
HGB-206: Peripheral blood VCN and HbA^{T87Q} over time





For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 36 study visit (N=2); Hb, hemoglobin; VCN, vector copy number

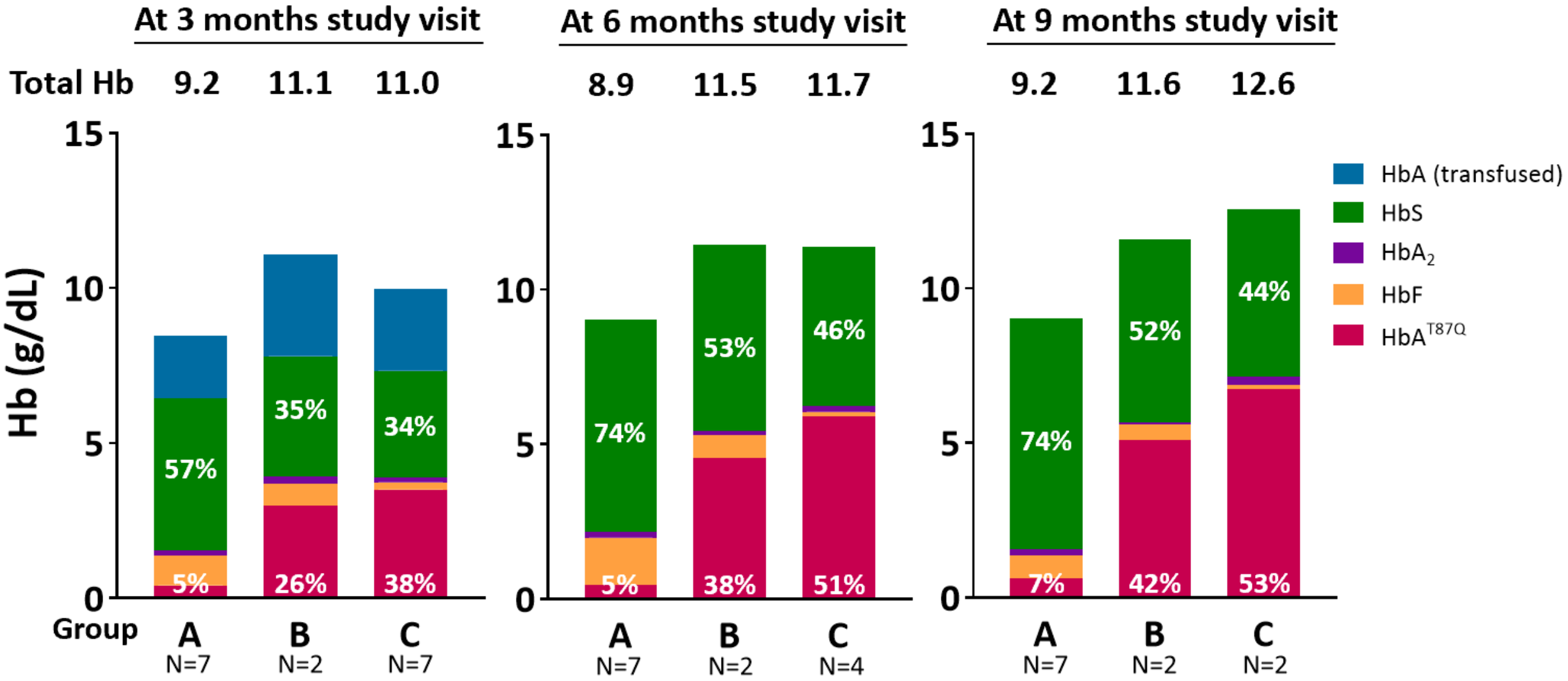
HGB-206: Total Hb levels over time



*N=2 at 36 months

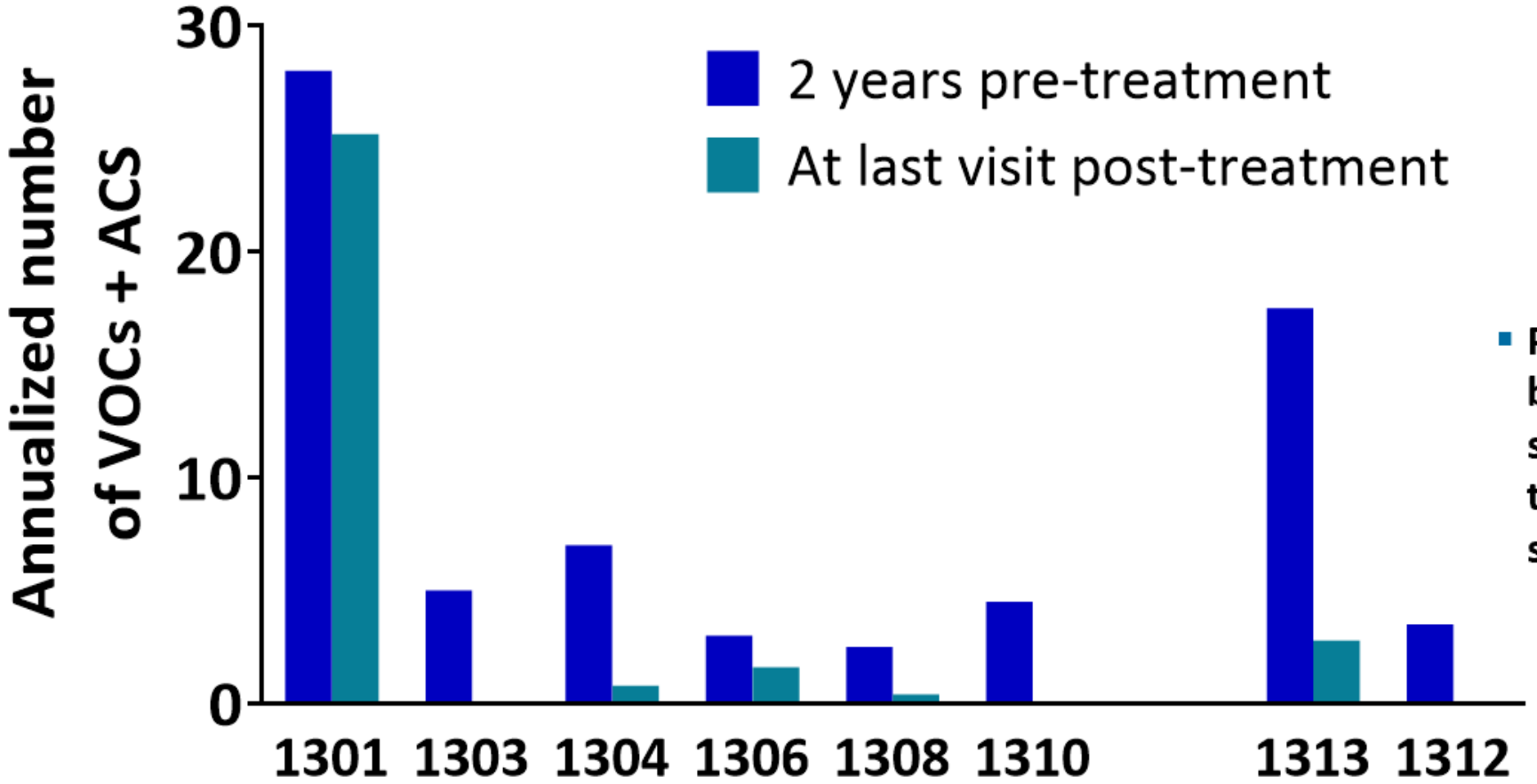
For Group A patients, medians (Q1, Q3) depicted; Hb, hemoglobin

HGB-206: Gene therapy-derived Hb (HbA^{T87Q}) equals or exceeds HbS levels at ≥ 3 months in Group C patients



% represent median Hb fractions as % of total; Hb, hemoglobin

HGB-206 Groups A and B: All patients have decreased rate of annualized VOCs plus ACS post-transplant



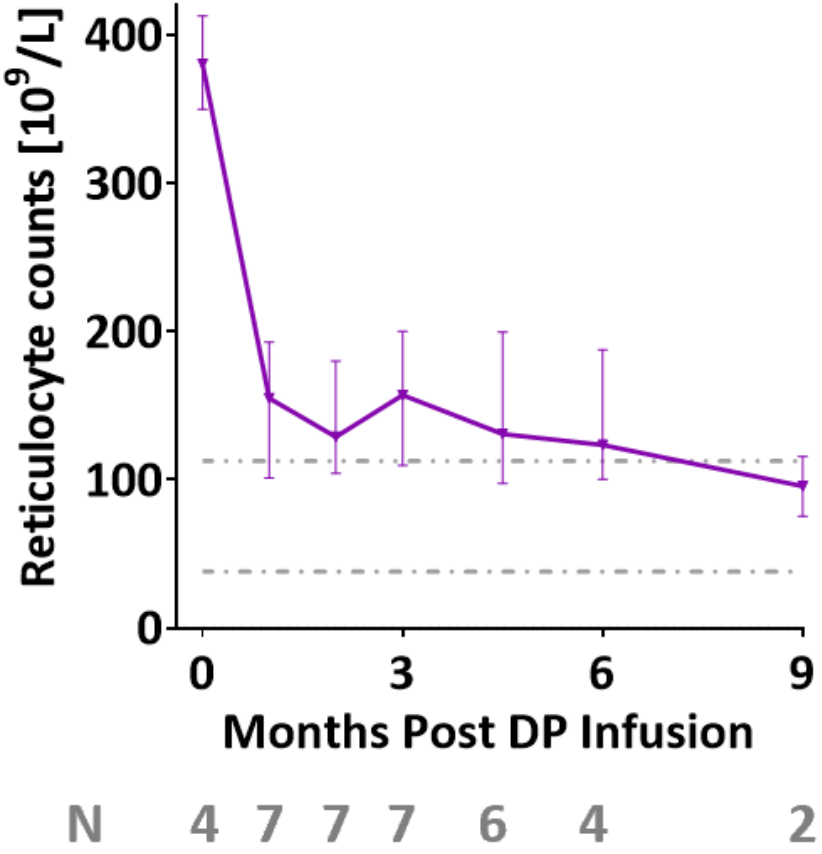
	1301	1303	1304	1306	1308	1310	1313	1312
% Decrease from baseline	10	100	89	46	84	100	84	100
Last study visit (Month)	36	36	30	30	30	30	18	15

Investigator-reported adverse events of VOC or ACS are shown

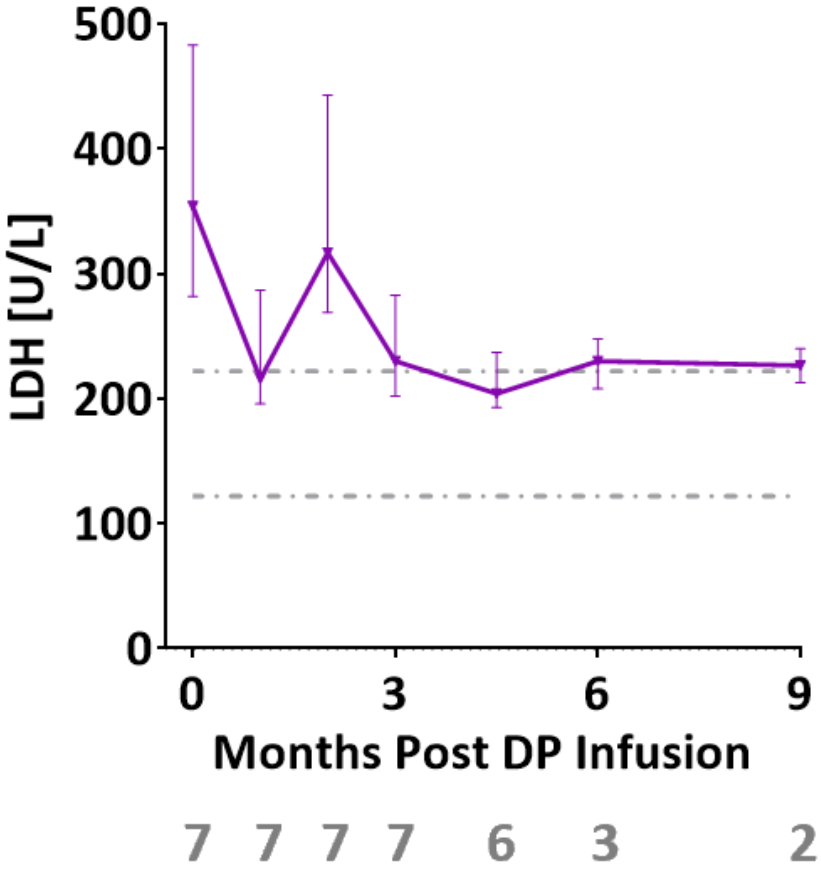
ACS, acute chest syndrome; RBC, red blood cell; VOCs, vaso-occlusive crises

HGB-206 Group C: Decreased hemolysis following LentiGlobin gene therapy

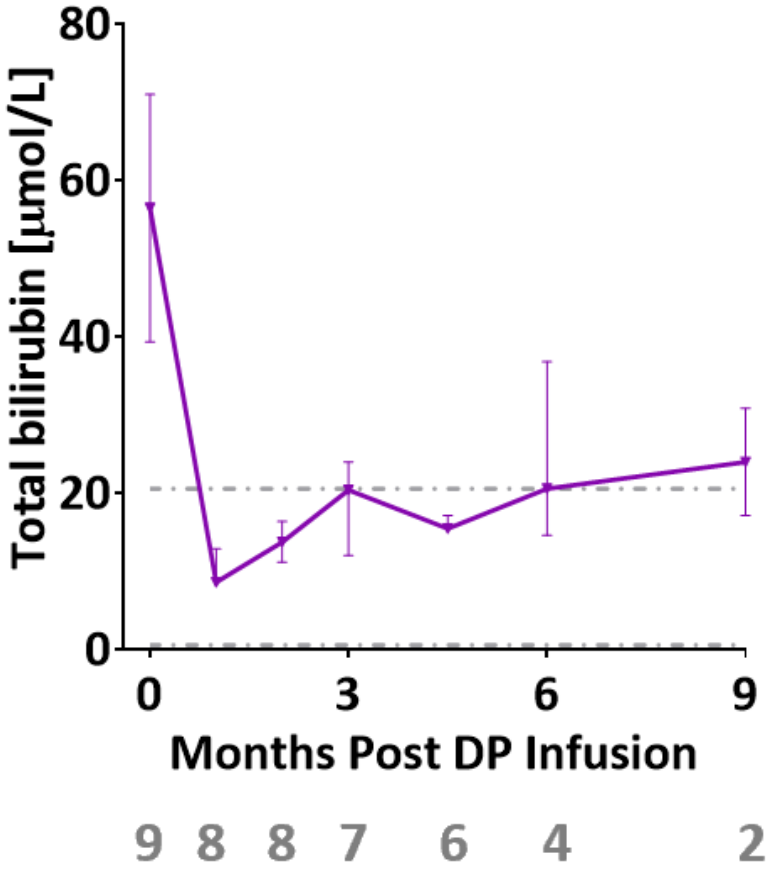
Reticulocyte Counts



Lactate Dehydrogenase



Total Bilirubin



Median (Q1, Q3) depicted; Dot-dash lines denote lower and upper limits of normal values

DP, drug product; LDH, lactate dehydrogenase

HGB-206: Summary

- Even modest HbA^{T87Q} levels (0.7-2.8 g/dL at last visit) can have clinical effect (reduced VOC plus ACS frequency)
- Refined manufacturing and other protocol modifications have improved results:
  - **Both Group B patients had increased HbA^{T87Q} levels (3.4 and 6.5 g/dL) and total Hb levels associated with 84 and 100% reduction in frequency of VOCs plus ACS**
  - **Group C demonstrates robust HbA^{T87Q} production of 4.8-8.8 g/dL at ≥ 6 months that equals or exceeds HbS levels**
    - Safety and feasibility of plerixafor mobilization and apheresis in SCD was shown
    - Hb of 9.9-13.7 g/dL at last visit without RBC transfusion
    - Decreased hemolysis after LentiGlobin gene therapy
- Safety profile of LentiGlobin gene therapy for severe SCD is consistent with myeloablative conditioning and underlying SCD
  - One case of MDS reported, not related to LentiGlobin gene therapy
- Protocol recently amended to
  - include adolescents and
  - further evaluate the clinical impact of LentiGlobin gene therapy in SCD

ACS, acute chest syndrome; Hb, hemoglobin; MDS, myelodysplastic syndrome; RBC, red blood cell; VOC, vaso-occlusive crisis

Updates to HGB-206: An open-label, multicenter phase 1/2 study of LentiGlobin for severe sickle cell disease

Enrollment Criteria: Group C

- ≥ 12 and ≤ 50 years of age
- At least 4 severe VOEs in the 24 months prior to consent
- Failure or intolerance to hydroxyurea

Target enrollment: 35 evaluable subjects

Study Endpoints: Group C

- Primary:
  - Globin Response
    - Weighted average HbA^{T87Q} ≥ 30% of total Hb AND
    - Weighted average total Hb increase of ≥ 3 g/dL compared to baseline total Hb OR weighted average total Hb ≥ 10 g/dL
- Key Secondary:
  - A 75% reduction in severe VOEs in 24 months following DP infusion

VOEs include acute episodes of pain, acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism (priapism episodes considered as long as medical attention was needed)

DP, drug product; Hb, hemoglobin; VOE, vaso-occlusive event

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