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UPDATED RESULTS FROM THE HGB-206 STUDY IN PATIENTS WITH SEVERE SICKLE CELL DISEASE TREATED UNDER A REVISED PROTOCOL WITH LENTIGLOBIN GENE THERAPY USING PLERIXAFOR-MOBILISED HAEMATOPOIETIC STEM CELLS

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DISCLOSURE OF AFFILIATIONS

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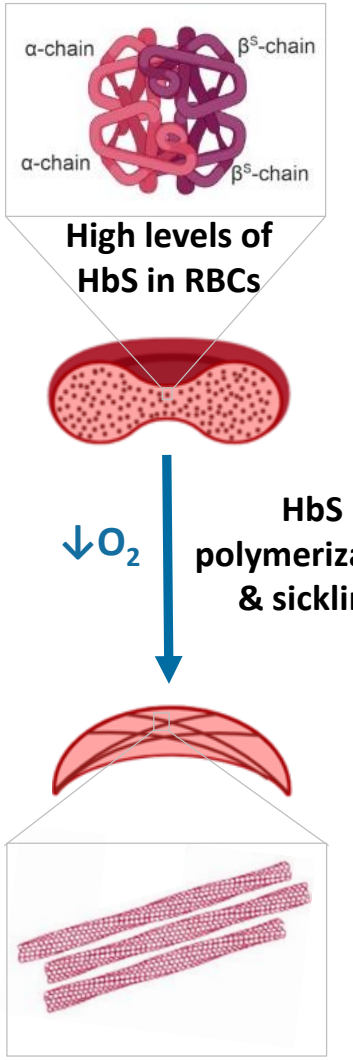
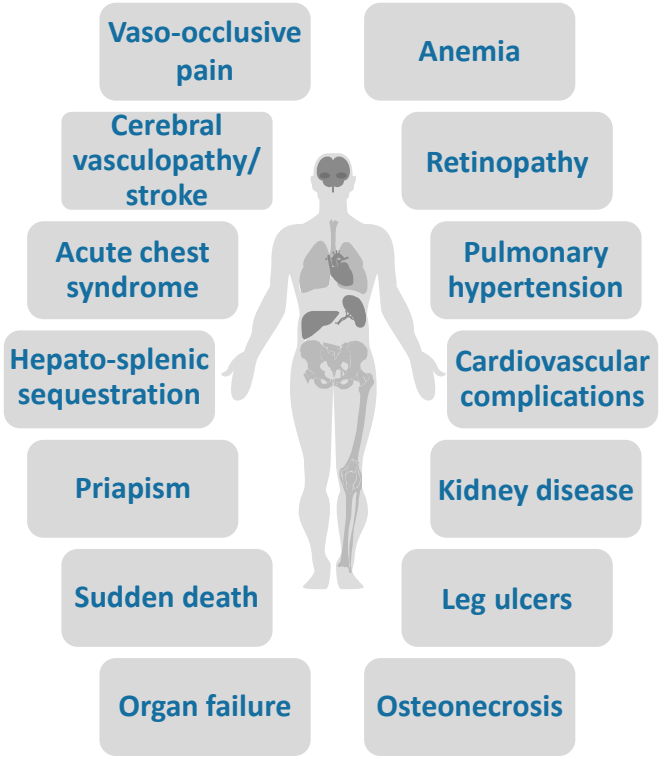
Discussion of off-label drug use: N/A

Sickle cell disease (SCD) is characterized by high morbidity and early mortality

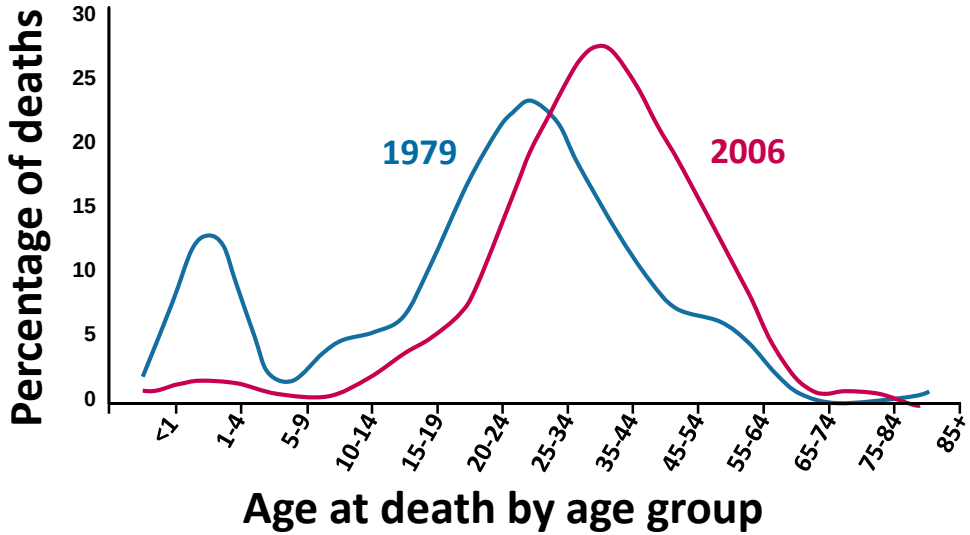


Vaso-occlusion
Hemolysis
Vasculopathy

Complications



> 50% of patients with SCD die before 45 years of age[1]



1. Hassell K., Am J Prev Med, 2010

Hb, hemoglobin; RBCs, red blood cells

HGB-206: An open-label, multicenter phase 1/2 study of LentiGlobin gene therapy in patients with severe SCD

HGB-206

Enrollment Criteria: Group C

- ≥ 12 and ≤ 50 years of age
- History of severe VOEs*
- Failure or intolerance to hydroxyurea

Key Outcomes: Group C

- HbA^{T87Q} ≥ 30% of total Hb
- Total Hb increase ≥ 3 g/dL compared to baseline OR total Hb ≥ 10 g/dL
- A 75% reduction in severe VOEs in 24 months following DP infusion

Target enrollment: 35 evaluable subjects

*Severe VOEs include hospitalization > 24 hours for acute episodes of pain, acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism (priapism episodes considered if medical facility visit was needed)

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

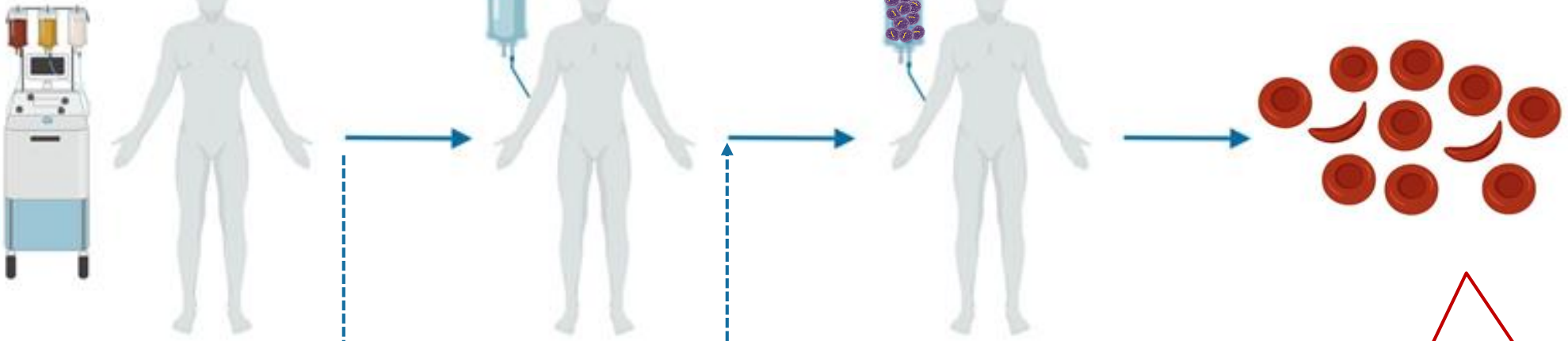
LentiGlobin for SCD gene therapy overview

HSC collection
Mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

DP infusion

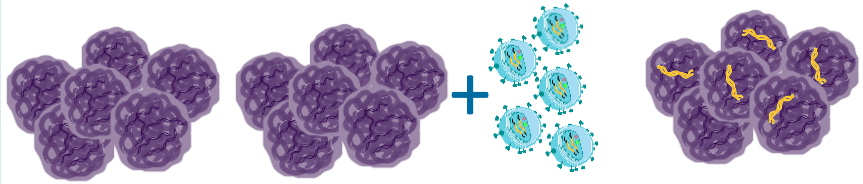
Transduced HSCs engraft and contribute to reconstitution of functional RBCs



2-yr follow-up

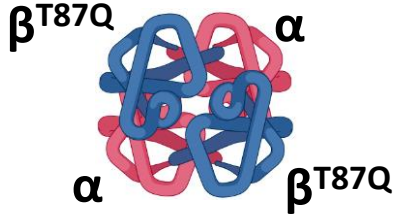
Long-Term Follow-Up Study

LentiGlobin DP centralized manufacturing



Select CD34+ cells *Transduce with BB305 lentiviral vector* *Cryopreserve, test, release DP*

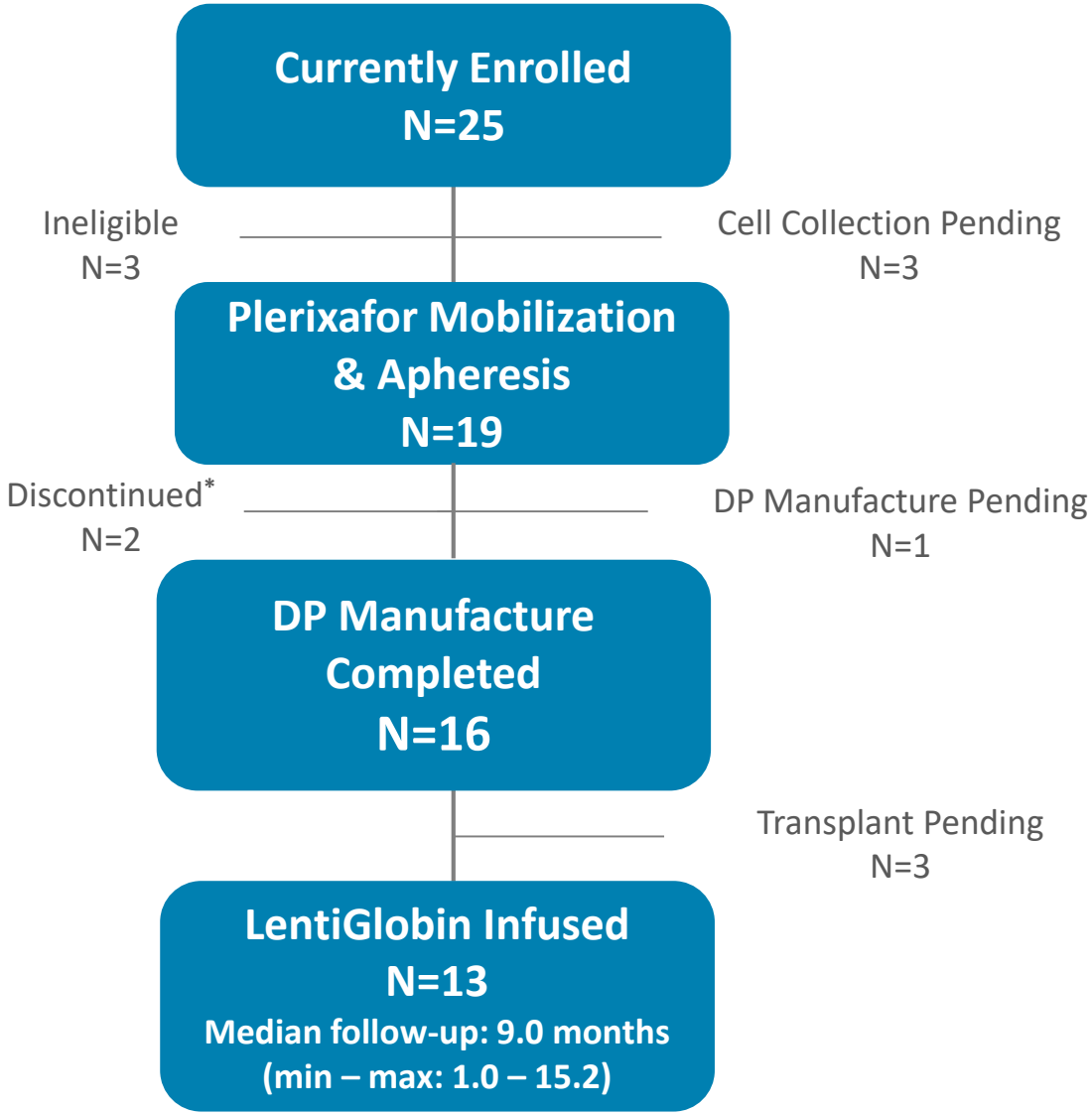
Modified RBCs express gene therapy-derived HbA^{T87Q}



DP, drug product; HSCs, hematopoietic stem cells; RBCs, red blood cells

HGB-206 Group C: Disposition

Currently enrolling



*1 withdrew consent, 1 discontinued due to investigator discretion; DP, drug product

HGB-206 Group C: Patient characteristics

N= 19 patients who started cell collection

Parameter	N=19
Age at consent, years median (min – max)	**26** (18 – 36)
Gender	**8F 11M**
Genotype, β^S/β^S	**19**
SCD History	
Hydroxyurea[*], n	**11**
VOCs[†], n Annualized no. of events, median (min – max)	**15** **4.0** (2.0 – 13.5)
ACS[‡], n Annualized no. of events, median (min – max)	**2** **1** (1 – 1)
Any history of stroke, n	**3**
TRJV > 2.5 m/s, n	**1**

[*]Within 30 days prior to informed consent; [†]≥ 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 Group C: Safety of plerixafor mobilization and apheresis

- **In 35 mobilization cycles in 19 patients, 7 Grade ≥ 3 AEs were reported in 5 patients**

Grade ≥ 3 AEs within 7 days of plerixafor administration	N=19 n (%)
Vaso-occlusive pain[1]	2 (10.5)
Hypomagnesaemia	2 (10.5)
Abdominal pain	1 (5.3)
Arthralgia	1 (5.3)
Non-cardiac chest pain	1 (5.3)

[1] The events were Grade 3, considered serious and consistent with patients' histories of vaso-occlusive pain. Patients were hospitalized, or hospitalization was prolonged for standard management. Both patients recovered without sequelae.

HGB-206 Group C: Treatment characteristics

N=13 infused patients

Parameter	N=13 Median (min – max)
No. of mobilization cycles	**2** (1 – 4)
CD34+ cells collected per mobilization cycle, x10^6 cells/kg	**10.1** (3.9 – 20.0)
Average busulfan AUC, µM*min	**4871** (4608 – 5182)
Follow-up, months	**9.0** (1.0 – 15.2)
Neutrophil engraftment, days (ANC ≥ 500 /µl)	**19** (15 – 24)†
Platelet engraftment, days (platelets > 50k /µl)	**28** (19 – 136)†
Duration of hospitalization‡, days	**36** (30 – 65)#

†n=12, 1 patient with 1 month follow-up had not engrafted at time of data cut-off; ‡Initiation of hospitalization from conditioning to discharge post-drug product infusion; #n=11, data not yet available for 2 patients, with 1 and 1.9 months of follow-up, respectively

- 12 patients had platelet engraftment by data cut-off, 11 in ≤ 90 days

ANC, absolute neutrophil count; AUC, area under the curve

HGB-206 Group C: Safety profile post-DP infusion generally consistent with myeloablative busulfan conditioning

Non-hematologic Grade ≥ 3 AEs *Post-DP infusion in ≥ 2 patients**	**N=13** **n (%)**
Febrile neutropenia	10 (77)
Stomatitis	7 (54)
Abdominal pain upper	2 (15)
Alanine aminotransferase increased	2 (15)
Blood bilirubin increased	2 (15)
Nausea	2 (15)
Serious AEs *Post-DP infusion in ≥ 2 patients*	**N=13** **n (%)**
Nausea	2 (15)
Vomiting	2 (15)

- No DP-related adverse events
- No cases of veno-occlusive liver disease
- No graft failure or deaths reported
- No vector-mediated RCL
- No evidence of clonal dominance

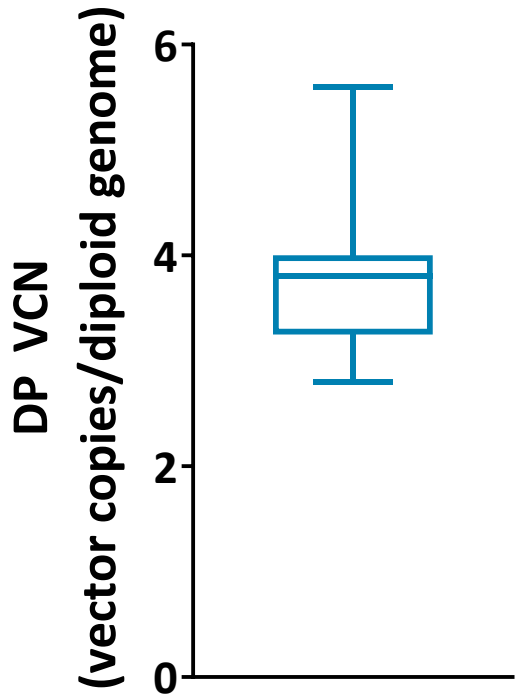
*Hematologic AEs commonly observed post-transplant have been excluded

AE, adverse event; DP, drug product; RCL, replication competent lentivirus

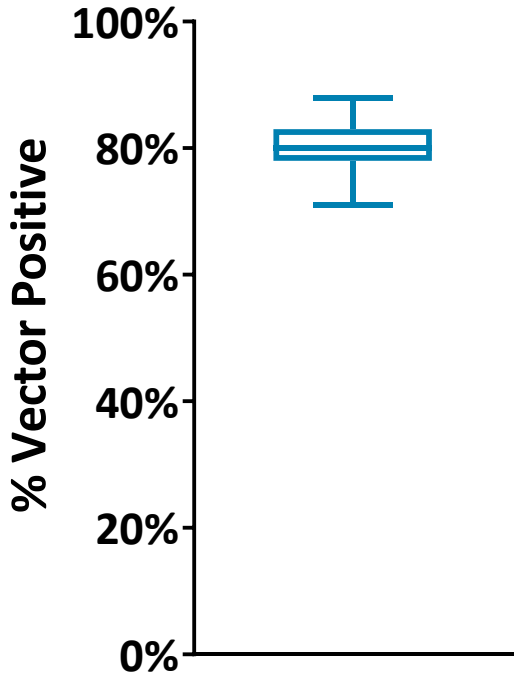
HGB-206 Group C: Drug product characteristics

N=13 infused patients

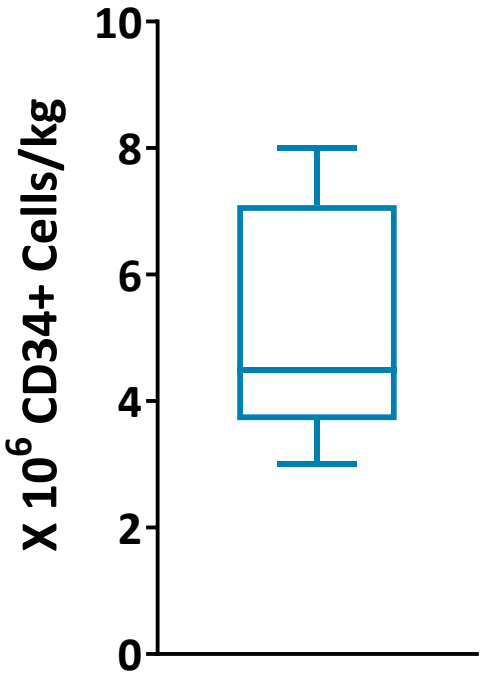
Vector copy number



% Transduced cells

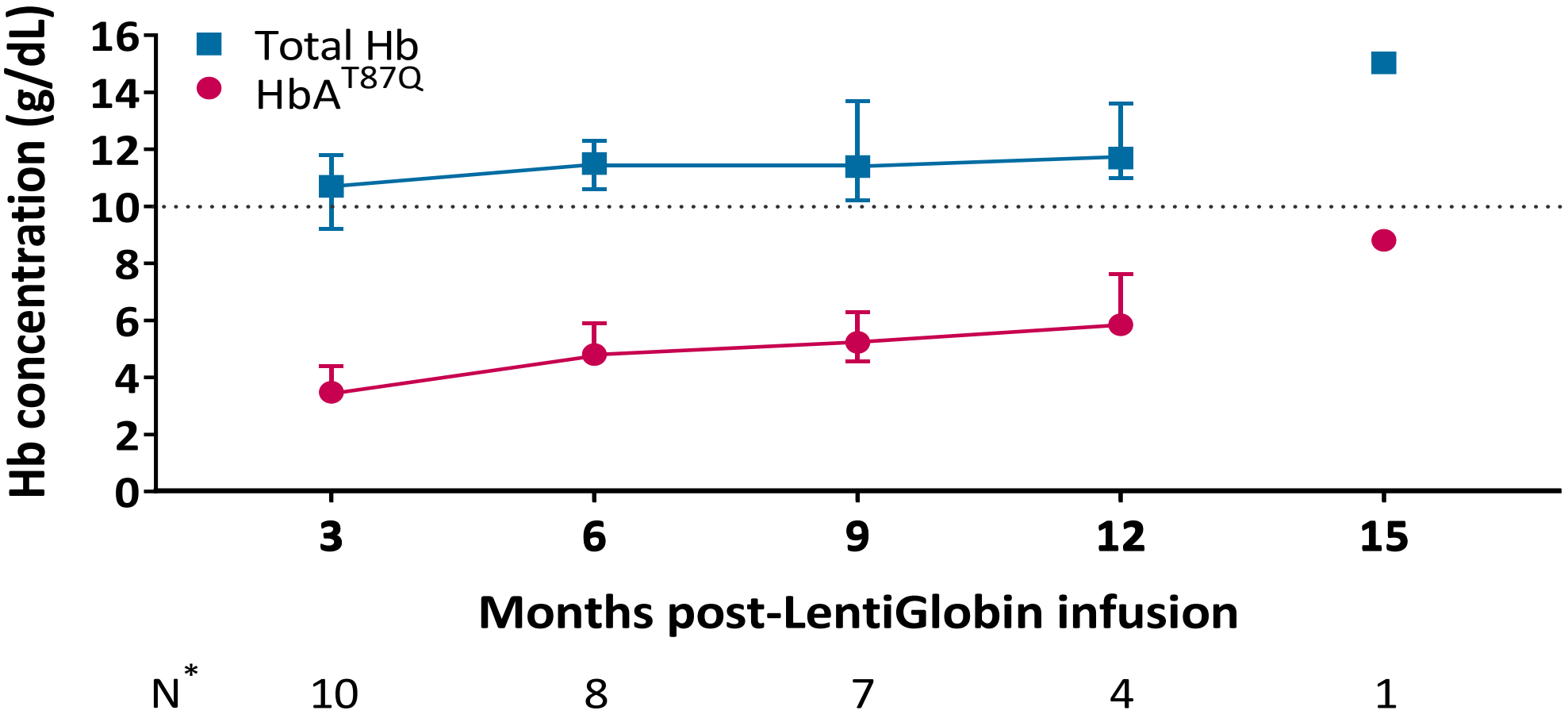


CD34+ cell dose



	Vector copy number	% Transduced cells	CD34+ cell dose
Median (min – max)	**3.8 (2.8 – 5.6)**	**80 (71 – 88)**	**4.5 (3.0 – 8.0)**

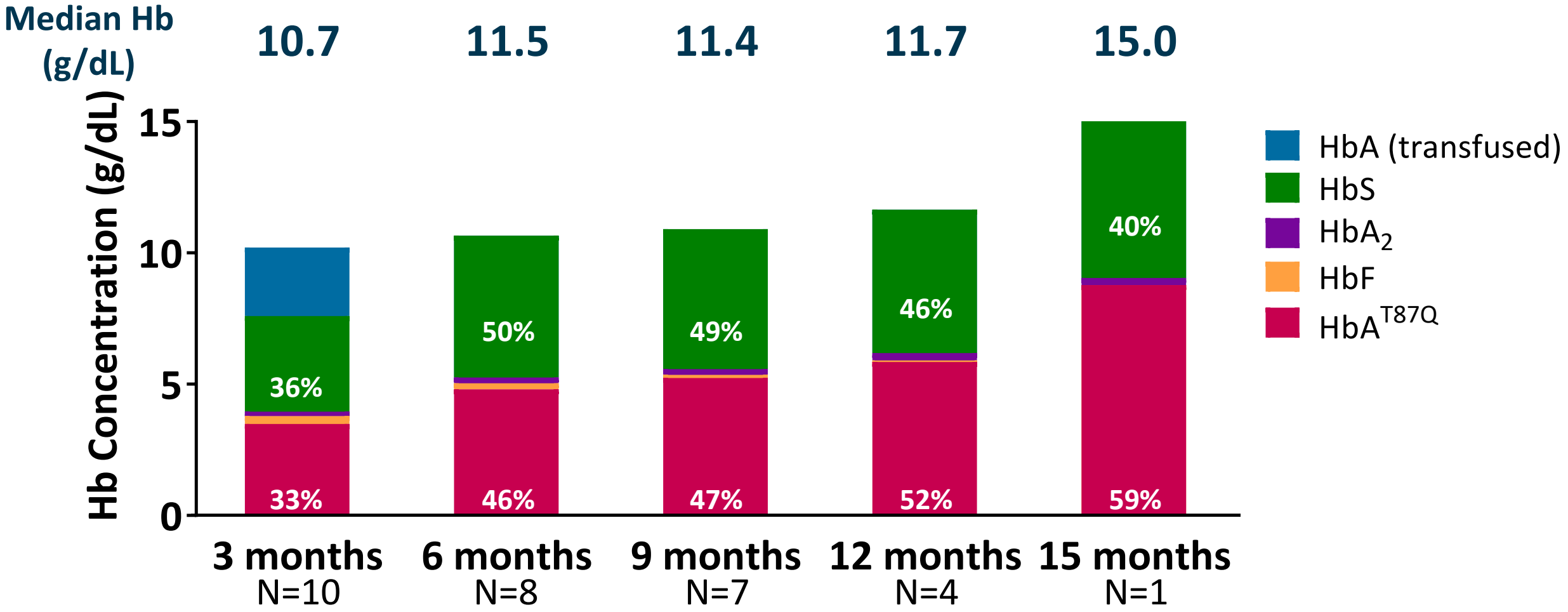
HGB-206 Group C: HbA^{T87Q} and total Hb over time



Median total Hb at screening was 9.4 (8.3 – 10.2) g/dL; includes some patients on chronic transfusions

Median (Q1, Q3) depicted; *Shows number of patients for whom data are available

HGB-206 Group C: Median HbS ≤ 50% at ≥ 6 months post-LentiGlobin treatment

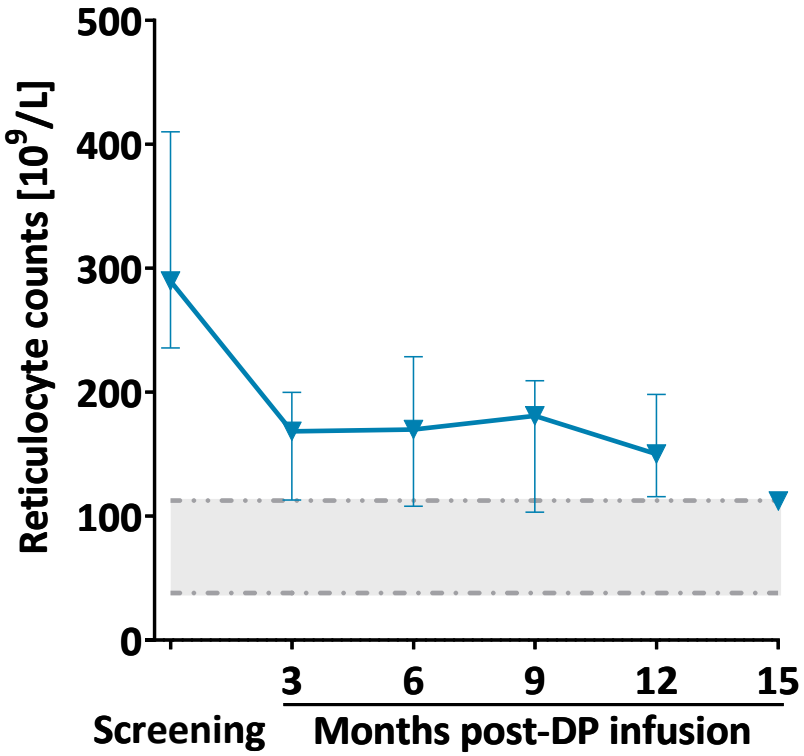


Total Hb and HbA^{T87Q} ranged from 10.2 – 15.0 g/dL and 4.5 – 8.8 g/dL, respectively, at last visit in patients with ≥ 6 months of follow-up

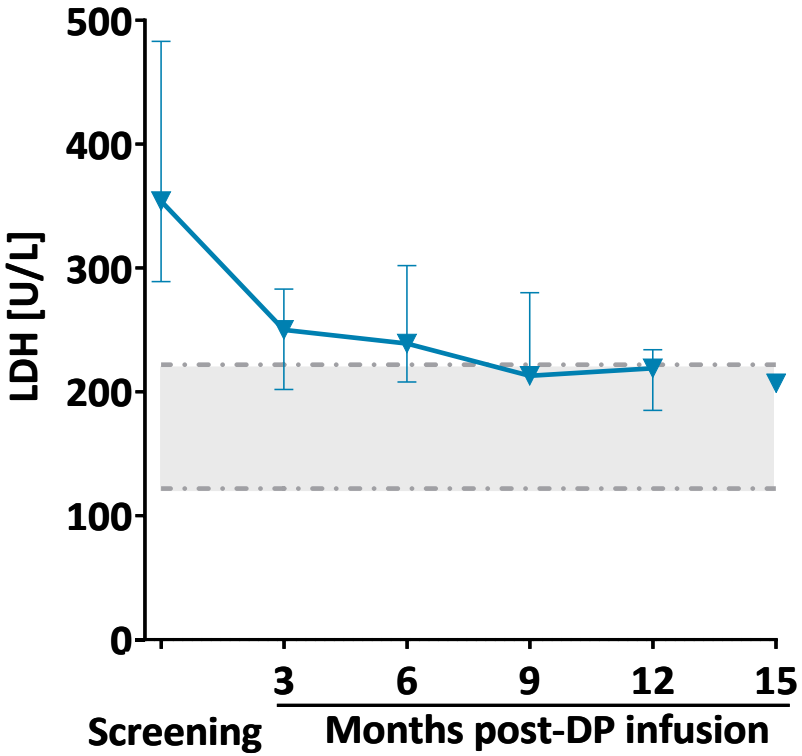
% represents median Hb fraction as % of total Hb; Hb, hemoglobin

HGB-206 Group C: Decreased hemolysis following LentiGlobin treatment

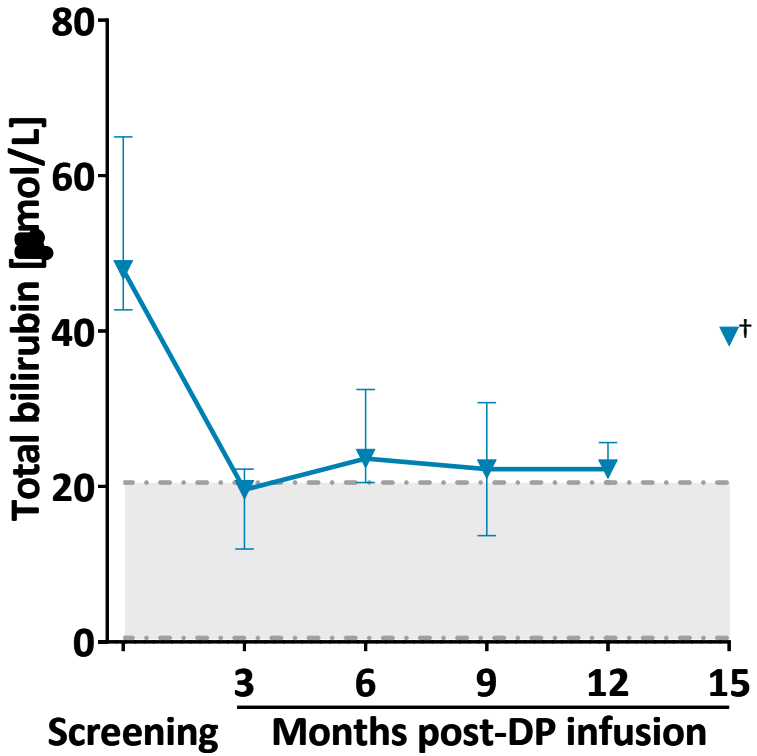
Reticulocyte Counts



Lactate Dehydrogenase



Total Bilirubin

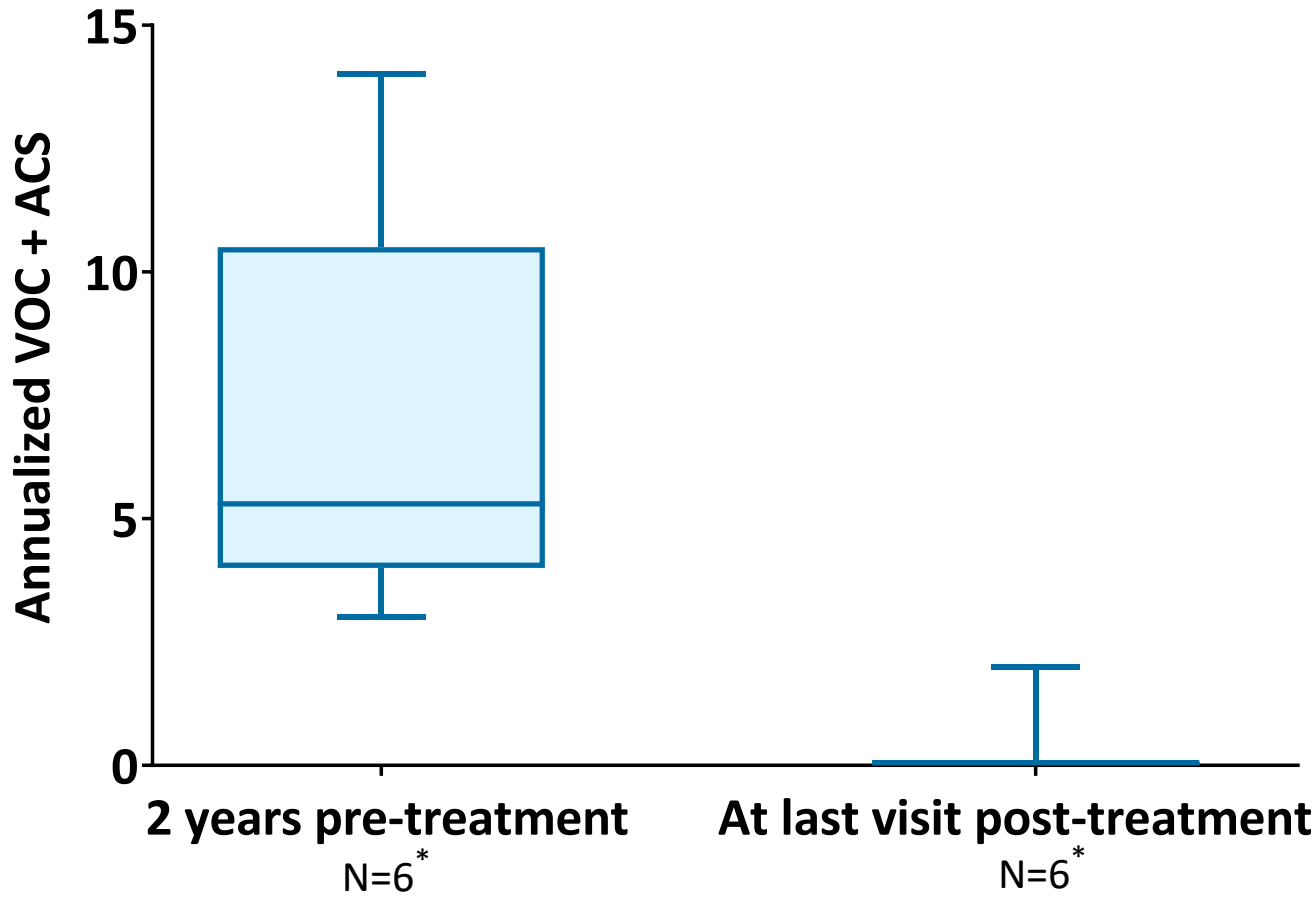


N*	13	10	8	7	5	1
	11	10	7	7	5	1
	13	10	8	7	5	1

Median (Q1, Q3) depicted; Dot-dash lines denote lower and upper limits of normal values; *Number of patients with data available; †Total bilirubin at last follow-up remains > 2-fold lower than at screening

DP, drug product; LDH, lactate dehydrogenase

HGB-206 Group C: Reduction in annualized rate of VOC + ACS post-treatment



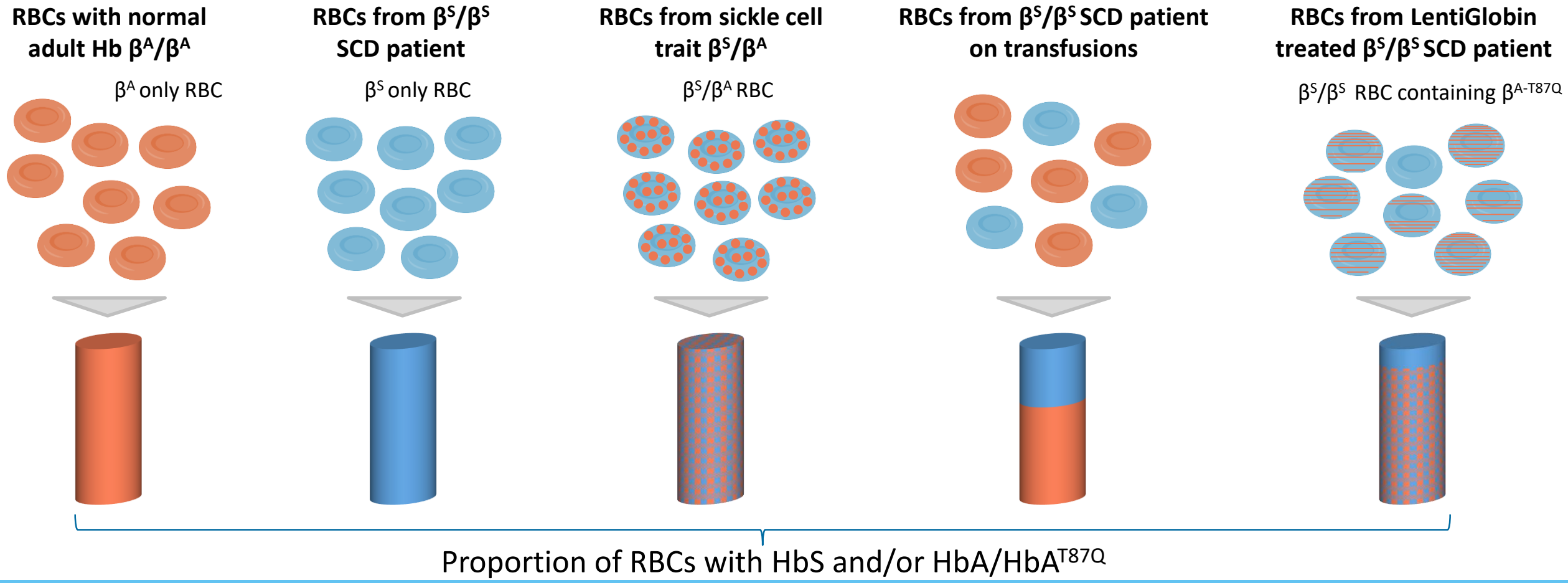
- **No ACS or serious VOCs occurred in any Group C patient post-LentiGlobin treatment to date**
- 1 non-serious Grade 2 VOC was observed in 1 patient ~3.5 months post-LentiGlobin treatment

Investigator-reported adverse events of VOC or ACS are shown; *Patients with ≥ 1 VOC/ACS in the 2 years before Informed Consent and with ~ ≥ 6 months of follow-up post-DP infusion

ACS, acute chest syndrome; DP, drug product; VOCs, vaso-occlusive crises

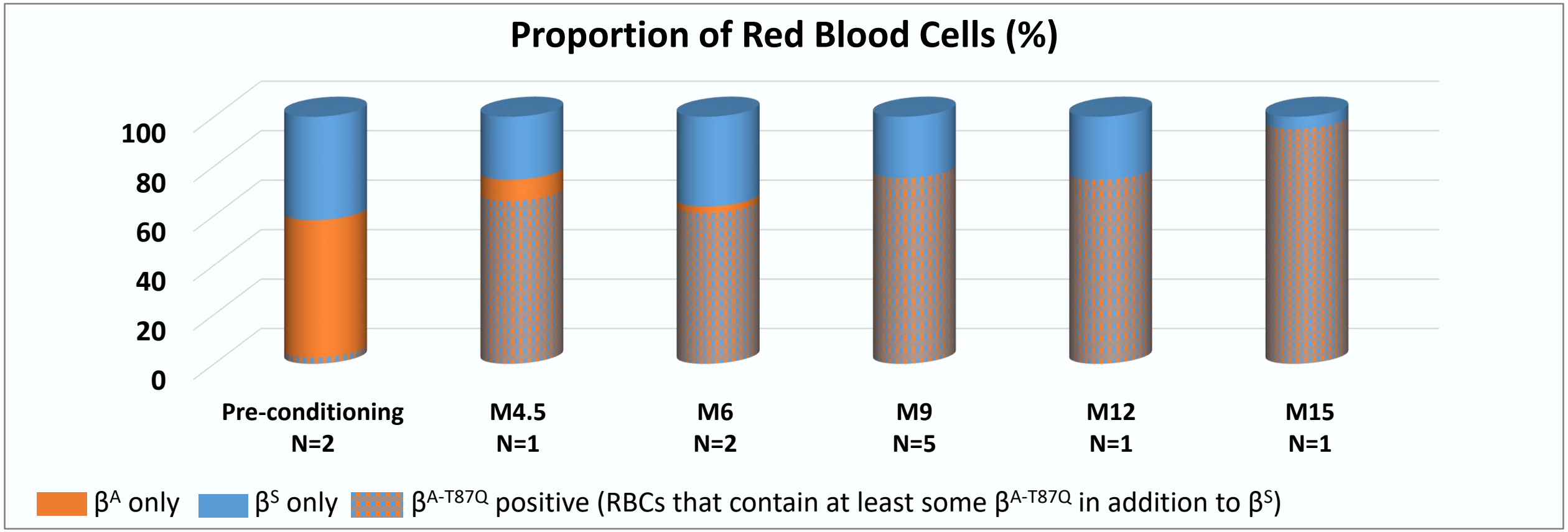
Exploratory assay allows for single-cell resolution of Hb expression to assess pancellularity of HbA^{T87Q}

- Exploratory assay: Single red blood cell western blot with anti-β^S or anti-$\beta^A/\beta^{A\text{-}T87Q}$ antibodies



HGB-206 Group C: On average, ≥ 70% of RBCs from patients treated with LentiGlobin contain $\beta^{A\text{-}T87Q}$ by month 9

- Single RBC western blot assay was performed in multiple patient samples



Mean is depicted - if N=1, data show technical replicates; *Pre-conditioning sample does not contain any $\beta^{A\text{-}T87Q}$, signal is due to error rate of multiples

RBCs, red blood cells

HGB-206 Group C: Summary

- Safety profile post-LentiGlobin gene therapy is generally consistent with myeloablative busulfan conditioning
- Group C drug products have consistently higher VCNs, proportion of transduced cells and cell dose
- No ACS or serious VOCs observed in Group C patients post-LentiGlobin treatment to date
- Robust expression of HbA^{T87Q} and median HbS ≤ 50% in patients with ≥ 6 months of follow-up
- Total unsupported Hb > 10 g/dL at last visit in patients with ≥ 6 months of follow-up and reduced hemolysis
- Data from an exploratory assay suggest that on average ≥ 70% of RBCs express HbA^{T87Q} by month 9
- Longer follow-up and recently expanded enrollment with modified endpoints will help further assess the clinical impact of LentiGlobin for SCD

ACS, acute chest syndrome; Hb, hemoglobin; VOC, vaso-occlusive crisis

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