Outcomes in Patients Treated With LentiGlobin for Sickle Cell Disease (SCD) Gene Therapy: Updated Results From the Phase 1/2 HGB-206 Group C Study

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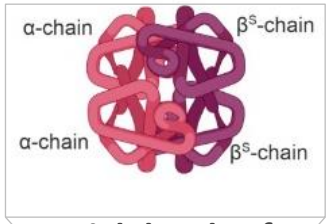
EBMT European Society for Blood and Marrow Transplantation

Disclosure

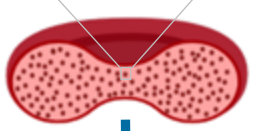
Markus Y. Mapara

Nothing to disclose

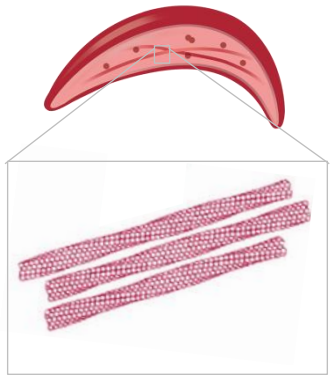
Sickle Cell Disease (SCD) is Characterized by High Morbidity and Early Mortality

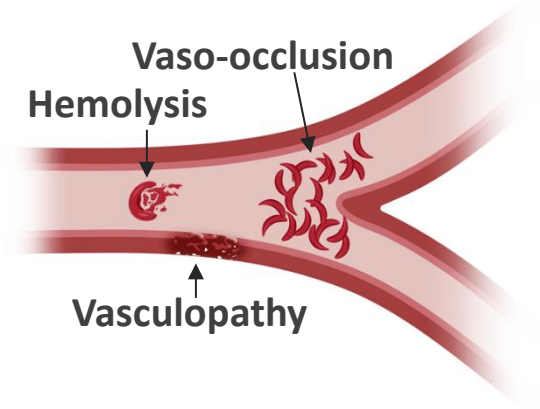


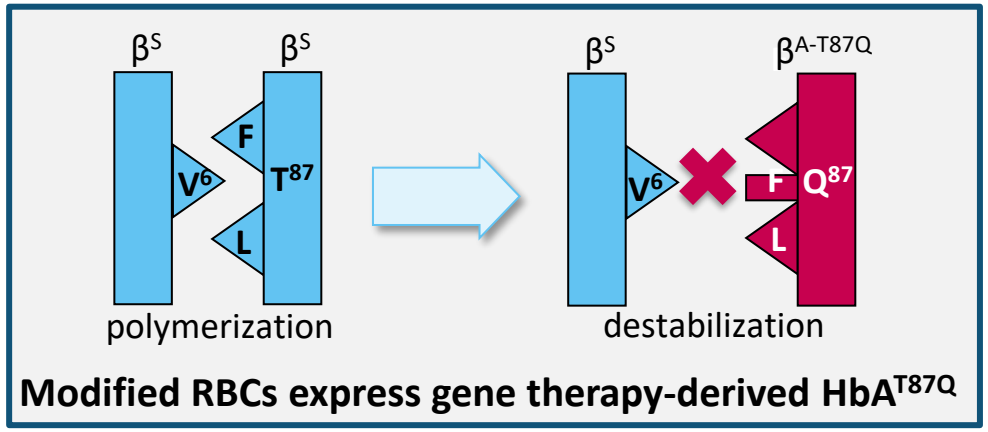
High levels of HbS in RBCs



↓O_2 HbS polymerization & sickling



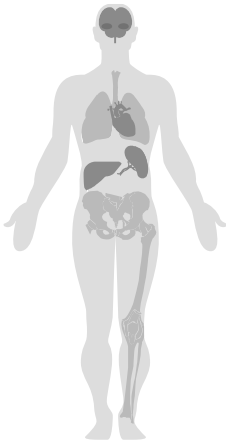




Modified RBCs express gene therapy-derived HbA^{T87Q}

Complications

- Vaso-occlusive pain
- Anemia
- Cerebral vasculopathy/ stroke
- Retinopathy
- Acute chest syndrome
- Pulmonary hypertension
- Hepato-splenic sequestration
- Cardiovascular complications
- Priapism
- Kidney disease
- Sudden death
- Leg ulcers
- Organ failure
- Osteonecrosis



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

- Death is often sudden[2,3]
- Common causes include failure of and damage to lung, heart, kidneys, and liver, as well as CNS disease, infections, thromboembolism, with or without acute pain complications[2-5]

1. Hassell K., Am J Prev Med 2010; 2. Darbari DS et al., AJH 2006; 3. Manci EA et al., BJH 2003; 4. Powars DR et al., Medicine (Baltimore) 2005; 5. Fitzhugh CD et al., AJH 2010; CNS, central nervous system; Hb, hemoglobin; RBC, red blood cell

HGB-206: An Open-Label, Multicenter Phase 1/2 Study of LentiGlobin for SCD (also known as bb1111) Gene Therapy in Patients with Severe SCD

HGB-206

Group C Enrollment Criteria

- ≥ 12 and ≤ 50 years of age
- $\beta^S\beta^S$, $\beta^S\beta^0$, $\beta^S\beta^+$ genotype
- History of severe VOEs*
- Failure or intolerance to hydroxyurea

Enrollment Completed

Group C Key Outcomes

- Weighted average HbA^{T87Q} ≥ 30% of total Hb for ≥ 6 months post-DP
- Weighted average: total Hb increase ≥ 3 g/dL vs baseline OR total Hb ≥ 10 g/dL for ≥ 6 months post-DP
- ≥ 75% reduction in severe VOEs in 24 months post-DP
- Complete resolution of severe VOEs

* Per inclusion criteria, severe VOEs include hospitalization or ER visit ≥ 24 hours or ≥ 2 visits to a day unit or ER over 72 hours, both requiring IV treatment, for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, acute splenic sequestration. Additionally, priapism events that require visit to medical care facility (without inpatient admission) are sufficient to meet severe VOE criterion

DP, drug product; ER, emergency room; Hb, hemoglobin; IV, intravenous; VOE, vaso-occlusive event

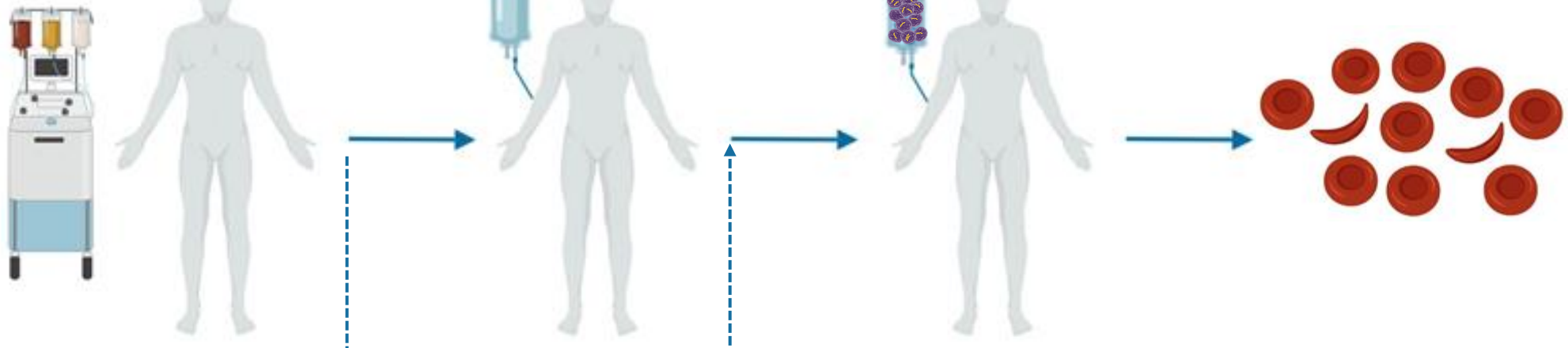
LentiGlobin for SCD Gene Therapy Overview

HSC collection
Mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

DP infusion

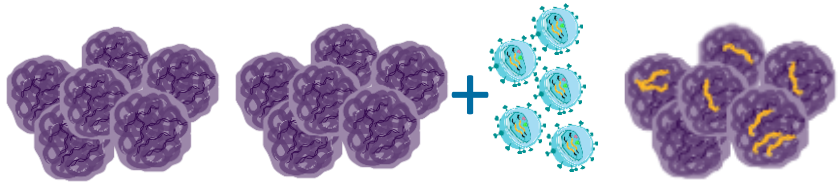
Transduced HSCs engraft and contribute to reconstitution of functional RBCs



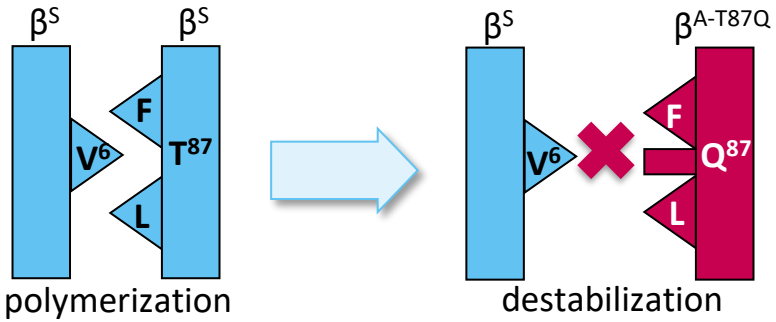
2-yr follow-up

Long-term follow-up study

LentiGlobin DP centralized manufacturing



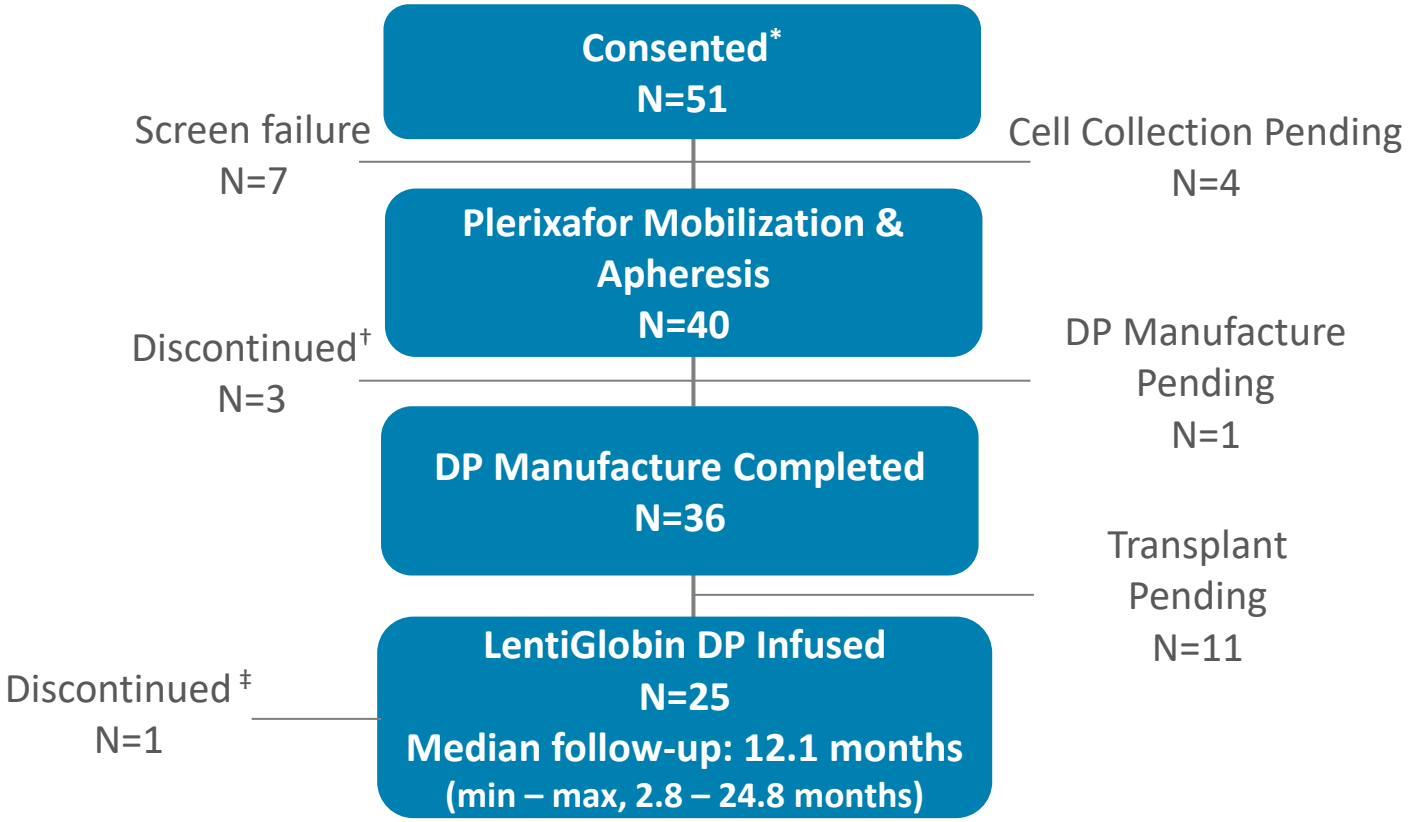
Select CD34+ cells ***Transduce with BB305 lentiviral vector*** ***Cryopreserve, test, release DP***



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

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

HGB-206 Group C: Study Disposition



* Currently active, not recruiting; † 1 withdrew consent, 1 at investigator discretion, 1 mobilization failure; ‡ 1 death

DP, drug product

HGB-206 Group C: Patient Characteristics for ITT Population

N=40 Patients who Started Cell Collection

Parameter	N=40
Age at consent, years, median (min – max)	**23.5** (12 – 38)
Age category	
18 – 50 years, n	**31**
12 – < 18 years, n	**9**
Gender, n	**16F 24M**
Genotype, n	**38** β^S/β^S **1** β^S/β^0 **1** β^S/β^+
SCD History	
VOCs[*], n	**32**[†]
Annualized no. of events, median (min – max)	**3.8** (2.0 – 33.0)
ACS[‡], n	**2**
Annualized no. of events, median (min – max)	**1** (1 – 1)
Any history of stroke, n	**6**

[*] ≥ 2 events/year in preceding 2 years; [†] Additional 4 patients have at least 4 VOEs in the 2 years prior to informed consent; [‡] ≥ 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; ITT, intent to treat; M, male; VOC, vaso-occlusive crisis; VOE, vaso-occlusive events

HGB-206 Group C: Treatment and Drug Product Characteristics

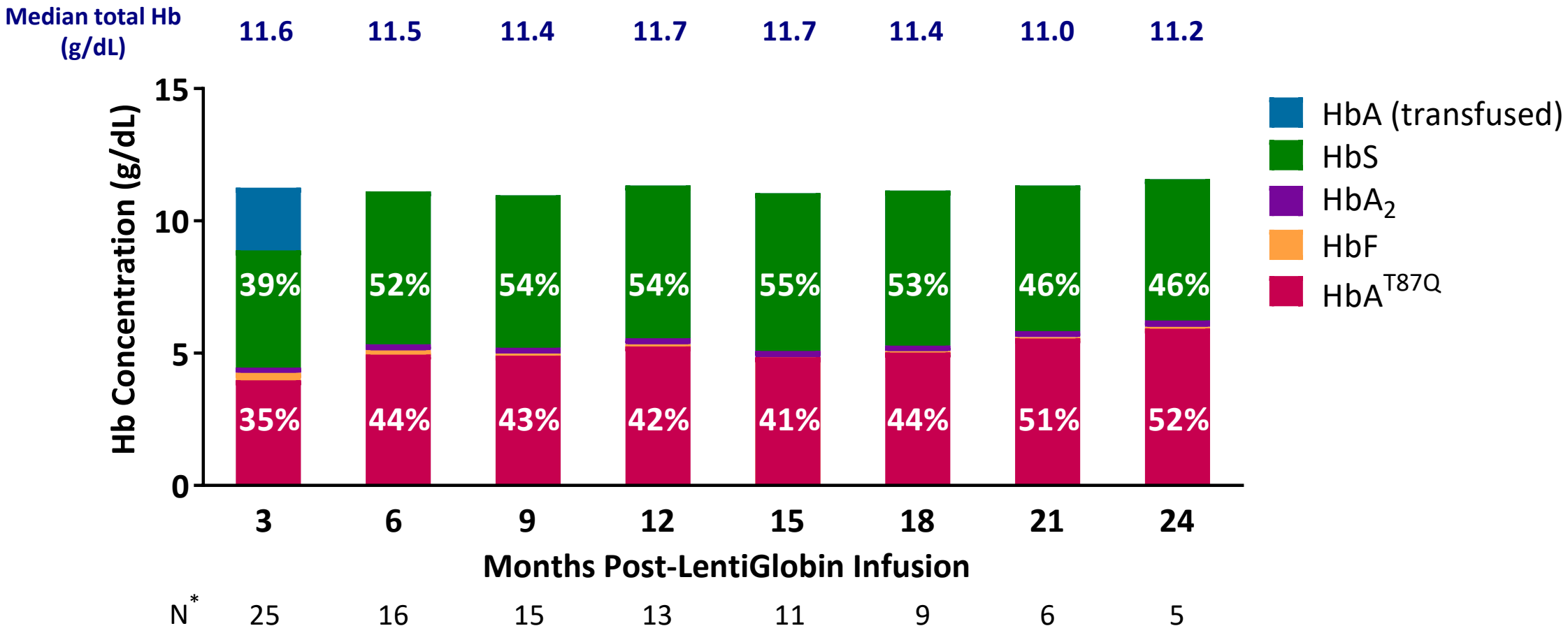
N=25 Infused Patients

Parameter	N=25 Median (min – max)
Treatment Characteristics	
No. of mobilization cycles	**2** (1 – 4)
CD34+ cells collected per mobilization cycle, x10^6 cells/kg	**10.3** (3.9 – 55.4)
Estimated average busulfan AUC, min*µmol/L[†]	**4873.5** (4288 – 7322)
Neutrophil engraftment, ANC ≥ 500 /µl x 3 days, days	**19** (12 – 27)
Platelet engraftment, platelets > 50k /µl x 3 days, days[‡]	**28** (19 – 136)
Duration of hospitalization[§], days	**35** (26 – 65)
Drug Product Characteristics (average per patient)	
Vector copy number, copies/diploid genome	**3.8** (2.3 – 5.7)
CD34+ cells transduced, %	**80** (63 – 93)
CD34+ cell dose, x10^6 cells/kg	**6.6** (3.0 – 16.0)

[†] 1 patient pending; [‡] 5 patients pending platelet engraftment at days 57, 57, 58, 60, and 65 post-DP infusion; [§] Duration of hospitalization from conditioning to discharge

ANC, absolute neutrophil count; AUC, area under the curve; DP, drug product

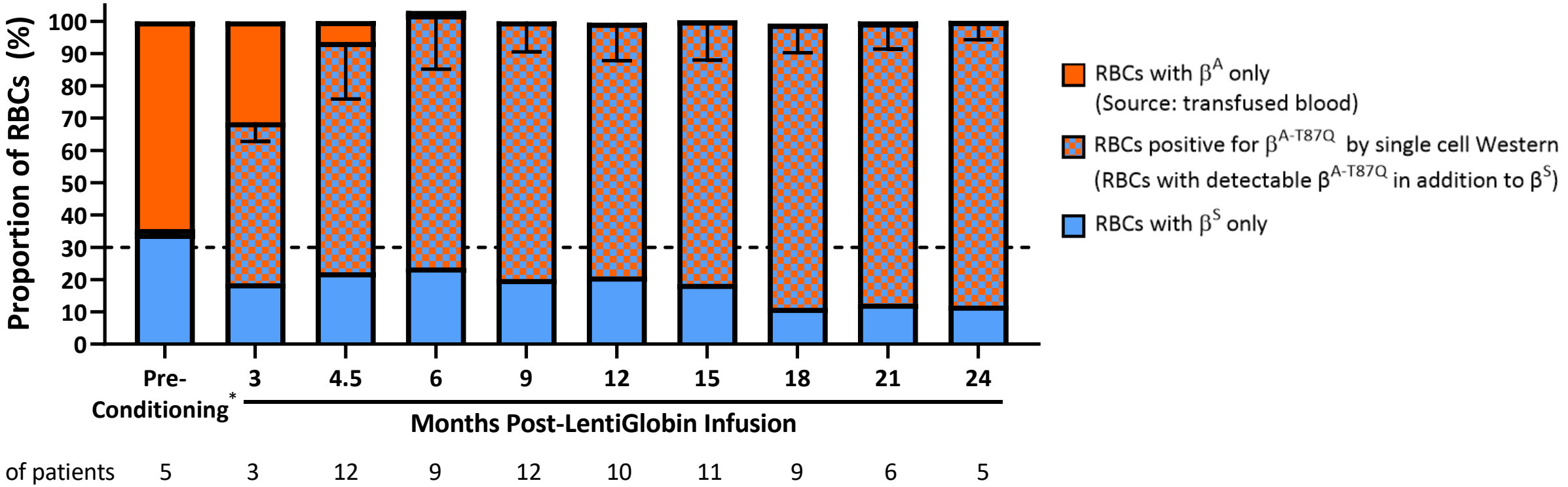
HGB-206 Group C: Median HbS ≤ 60% and HbA^{T87Q} ≥ 40% at ≥ 6 Months Post-LentiGlobin Treatment



% represents median Hb fraction as % of total Hb; * Number of patients with data available; Hb, hemoglobin

Average Proportion of RBCs Containing $\beta^{A\text{-}T87Q}$ from LentiGlobin-Treated Patients is ≥ 70% by Month 6 and ~90% by Month 18

- Single RBC western assay was performed in a subset of HGB-206 Group C patient samples



N of patients	5	3	12	9	12	10	11	9	6	5

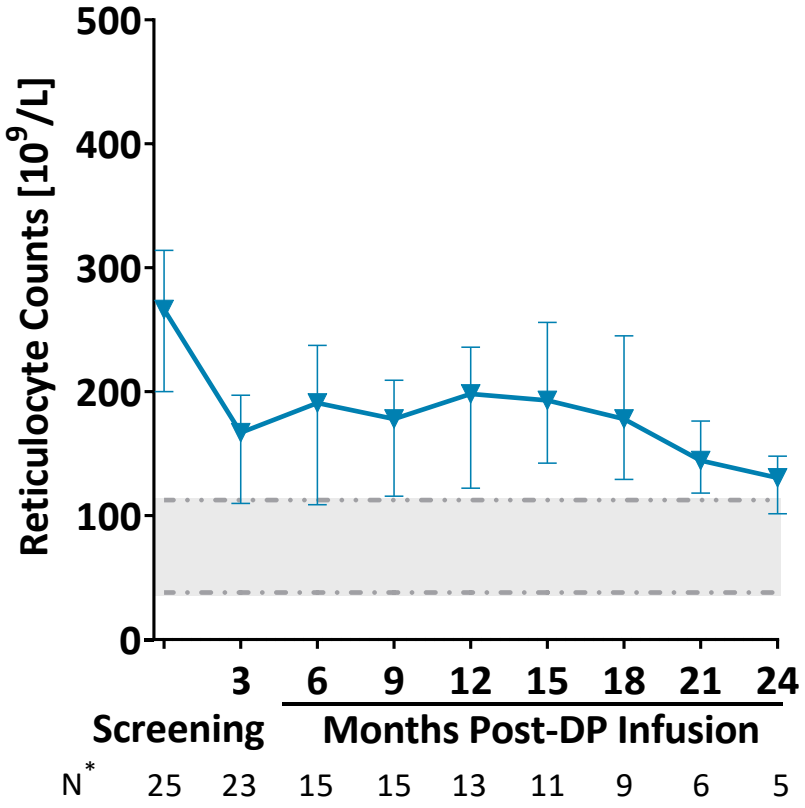
- **Median (min – max) HbA^{T87Q}/RBC was 15.3 (11.7 – 20)† pg in patients with ≥ 6 months follow-up, which is comparable to the 13 – 18 pg of HbA/RBC in individuals with sickle cell trait‡ and higher than 10 pg of HbF/RBC in those with HPFH§**

Mean & SD are depicted; Reducing HbS to < 30% is recommended by guidelines for exchange RBC transfusions for patients with SCD (indicated by dashed line);* Pre-conditioning sample does not contain any $\beta^{A\text{-}T87Q}$, signal is due to error rate of multiples; † Calculated as (% HbA^{T87Q} of total Hb/% RBCs containing $\beta^{A\text{-}T87Q}$) x MCH; ‡ Calculated to 13-18 pg HbA/RBC using 50% HbA/RBC for the lower end of the range and 60% HbA/RBC for the upper end of the range; § Estimated in Steinberg MH et al., Blood 2014

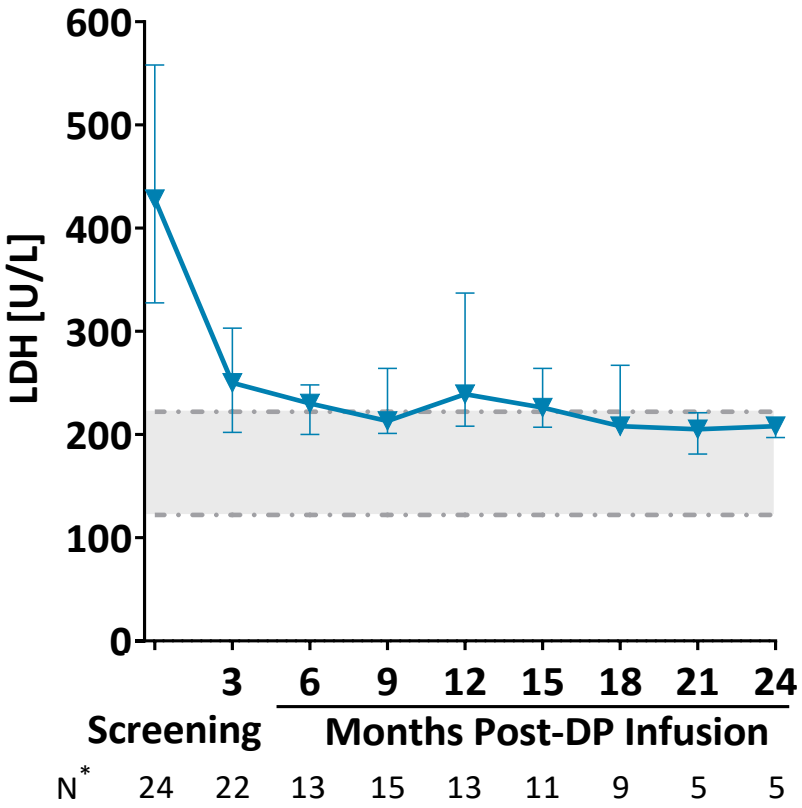
Hb, hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; MCH, mean corpuscular hemoglobin; RBCs, red blood cells; SD, standard deviation

HGB-206 Group C: Decrease in Hemolysis Markers Post-LentiGlobin Treatment

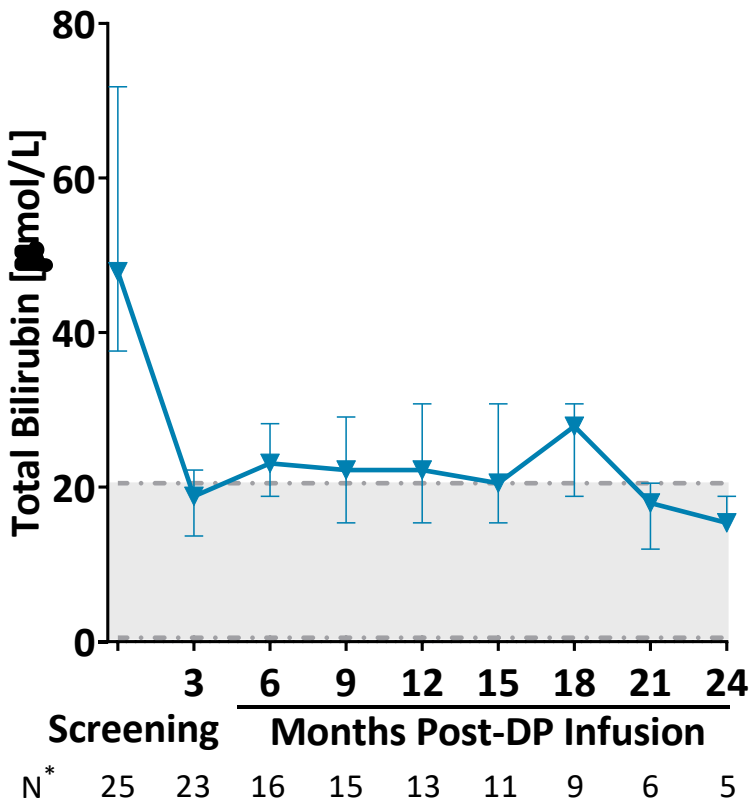
Reticulocyte Counts



Lactate Dehydrogenase

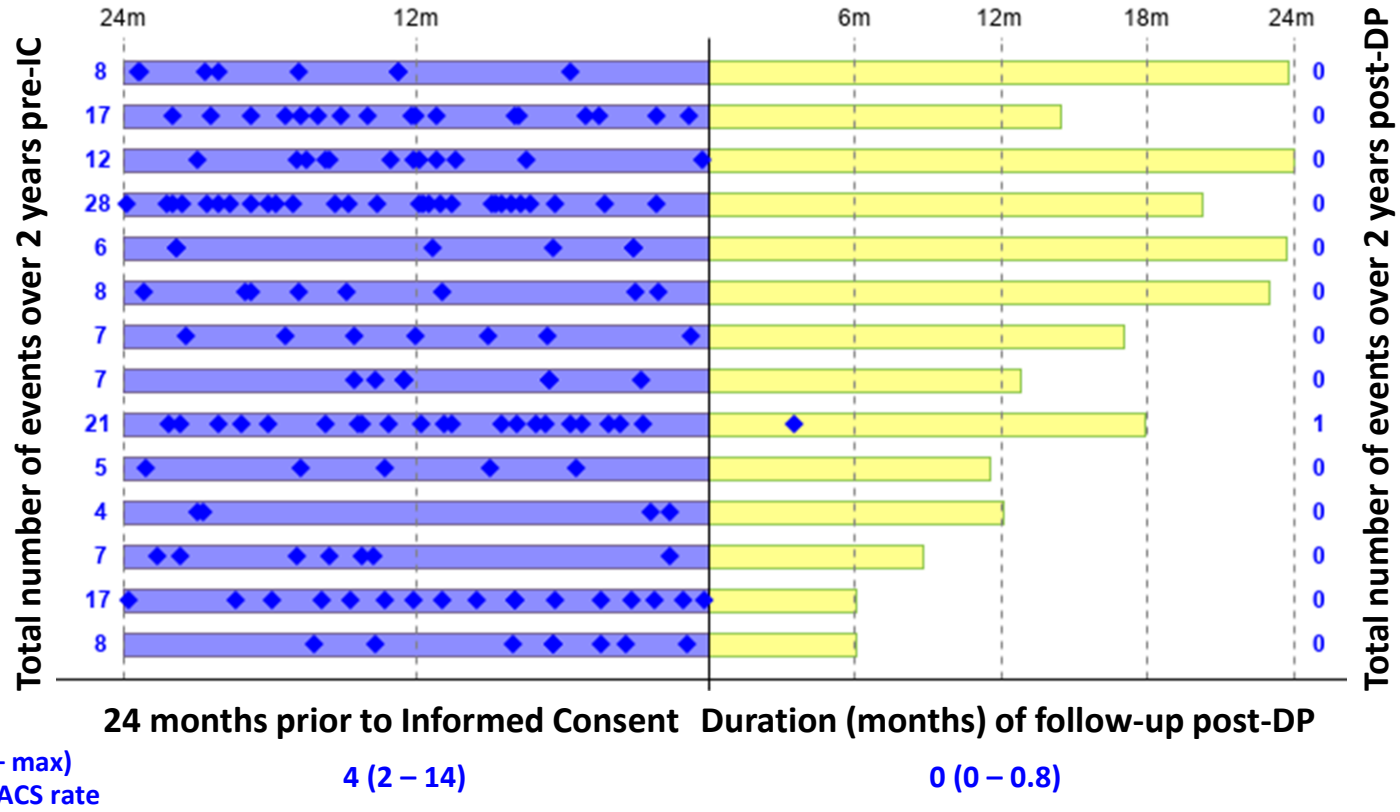


Total Bilirubin



Median (Q1, Q3) depicted; Dot-dash lines denote lower and upper limits of normal values; * Number of patients with data available; LDH, lactate dehydrogenase

HGB-206 Group C: Reduction of VOC+ACS Post-LentiGlobin Treatment



- The mean reduction of annualized VOC+ACS rate post-LentiGlobin treatment is 99.5% [95% CI, 92.4 – 100%]
- No ACS or serious VOCs occurred in any Group C patient post-LentiGlobin treatment to date (2.8 – 24.8 months follow-up)
- 1 non-serious Grade 2 VOC was observed in 1 patient ~ 3.5 months post-LentiGlobin treatment

Investigator-reported AEs of VOC or ACS are shown; Patients with ≥ 4 VOC/ACS at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included
ACS, acute chest syndrome; CI, confidence interval; DP, drug product; IC, informed consent; VOC, vaso-occlusive crisis

HGB-206 Group C: Safety Profile Post-LentiGlobin Infusion

Non-hematologic ≥ Grade 3 AEs *Post-DP infusion in ≥ 2 patients*[*]	**N=25** n (%)
Stomatitis	15 (60)
Febrile neutropenia	11 (44)
Increased ALT	3 (12)
Increased AST	3 (12)
Increased GGT	3 (12)
Increased total bilirubin	3 (12)
Nausea	3 (12)
Premature menopause	2 (8)
Upper abdominal pain	2 (8)
Serious AEs *Post-DP infusion in ≥ 2 patients*	
Nausea	2 (8)
Opioid withdrawal syndrome	2 (8)
Vomiting	2 (8)

[*] Hematologic AEs commonly observed post-transplantation have been excluded; AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase

- 3 patients with DP-related AEs (all non-serious and ≤ Grade 2)[†]
- No cases of veno-occlusive liver disease
- No graft failure
- No vector-mediated RCL and no insertional oncogenesis
- One death, unlikely related to LentiGlobin: A 27-year-old patient with history of VOC/ACS, pulmonary hypertension, and venous thrombosis died ~20 months post-treatment after sudden onset of shortness of breath followed by cardiac arrest
  - Post-DP: No VOCs/ACS (vs 28 episodes in 2 years pre-study); no sickle-related adverse events or ≥ Grade 3 AEs
    - At last study visit, Hb was 13.9 g/dL, with HbA^{T87Q} 36% and HbS 56%
  - Autopsy showed no evidence of pulmonary embolism, stroke, or clinically significant sickling
    - Death was due to CV disease, with findings of cardiomegaly, cardiac fibrosis, and pulmonary congestion
  - Per PIs, pre-existing SCD-related cardiac disease and pulmonary hypertension may have been contributing factors

[†] 1 pt with Grade 2 nonserious neutropenic fever on study day 10 (resolved on study day 18); 1 pt with post-DP infusion Grade 2 AEs of nail discoloration and constipation as well as Grade 1 AEs of runny nose and cough. This pt also had 3 AEs with onset pre-DP infusion (nonserious Grade 2 alopecia, Grade 1 vomiting and Grade 1 fatigue) which were initially assessed as DP-related, but attribution was changed to not DP-related after datacut date; 1 pt with 1 event of nonserious Grade 2 back pain

ACS, acute chest syndrome; CV, cardiovascular; DP, drug product; Hb, hemoglobin; PIs, principal investigators; RCL, replication competent lentivirus; VOC, vaso-occlusive crisis

HGB-206 Group C: Summary

- Mean reduction of 99.5% [95% CI, 92.4 – 100%] in annualized VOC+ACS rate post-LentiGlobin; no serious VOCs or ACS with up to 24 months of follow-up
- In patients with ≥ 6 months of follow-up, median total unsupported Hb was ≥ 11 g/dL, with a median HbS ≤ 60% and a median anti-sickling HbA^{T87Q} ≥ 40%
- Near pancellular expression of HbA^{T87Q} ≥ 6 months post-LentiGlobin, with on average ~90% of RBCs containing HbA^{T87Q} at ≥ 18 months post-treatment; amounts of HbA^{T87Q}/RBC comparable to the HbA/RBC in sickle cell trait
- Treatment with LentiGlobin decreased key markers of hemolysis
- The safety profile post-LentiGlobin for SCD gene therapy remains generally consistent with myeloablative single-agent busulfan conditioning and underlying SCD
  - One death unlikely related to DP > 18 months post-LentiGlobin in a patient with significant baseline SCD-related cardiopulmonary disease
- The primary endpoint supporting BLA submission for LentiGlobin for SCD will be complete resolution of severe VOEs evaluated in patients treated in HGB-206 Group C with ≥ 18 months of follow-up

* Per inclusion criteria, severe VOEs include hospitalization or emergency room visit ≥24 hours or ≥2 visits to a day unit or ER over 72 hours, both requiring intravenous treatment, for the following: acute episodes of pain, acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism (priapism episodes considered if medical facility visit was needed)

ACS, acute chest syndrome; BLA, biologics license application; CI, confidence interval; DP, drug product; Hb, hemoglobin; RBCs, red blood cells; VOC, vaso-occlusive crisis; VOE, vaso-occlusive event

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