Resolution of Serious Vaso-Occlusive Pain Crises and Reduction in Patient-Reported Pain Intensity: Results from the Ongoing Phase 1/2 HGB-206 Group C Study of LentiGlobin for Sickle Cell Disease (bb1111) Gene Therapy

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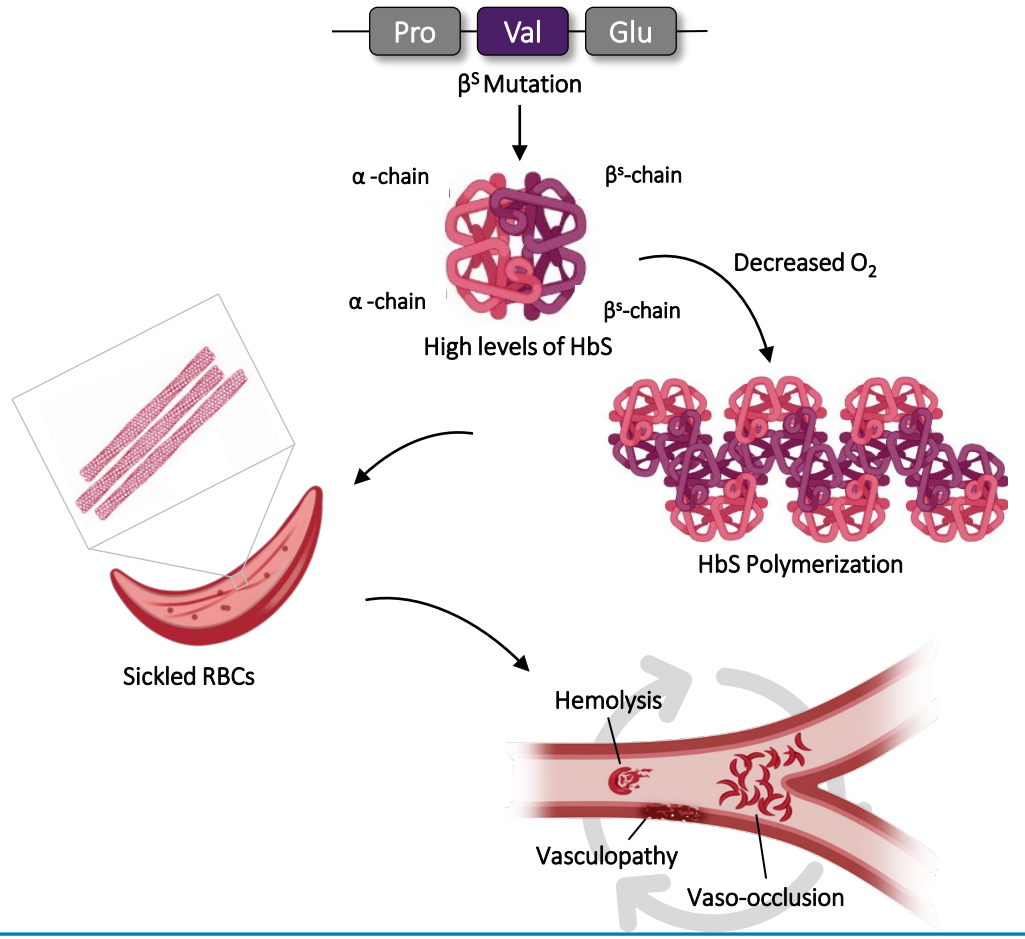
Sickle cell disease is characterized by high morbidity and early mortality

Pathophysiology of SCD[1]



Complications[2,3]

- Chronic daily pain
- 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[2]

1. Kato GJ, et al. Nat Rev Dis Primer. 2018;4:18010; 2. Hassell K., Am J Prev Med 2010; 3. Kanter, et al. Blood Rev. 2013;27(6):279- 287; Glu, glutamic acid; Hbs, sickle hemoglobin; Pro, proline; RBC, red blood cell; SCD, sickle cell disease; Val, valine.

HGB-206: An open-label, multicenter, phase 1/2 study of LentiGlobin gene therapy (bb1111) in patients with severe SCD

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*
- Hydroxyurea failure or intolerance

Enrollment Completed
(NCT02140554)

Group C Key Outcomes

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

*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, and 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; SCD, sickle cell disease; VOE, vaso-occlusive event.

LentiGlobin for SCD gene therapy overview

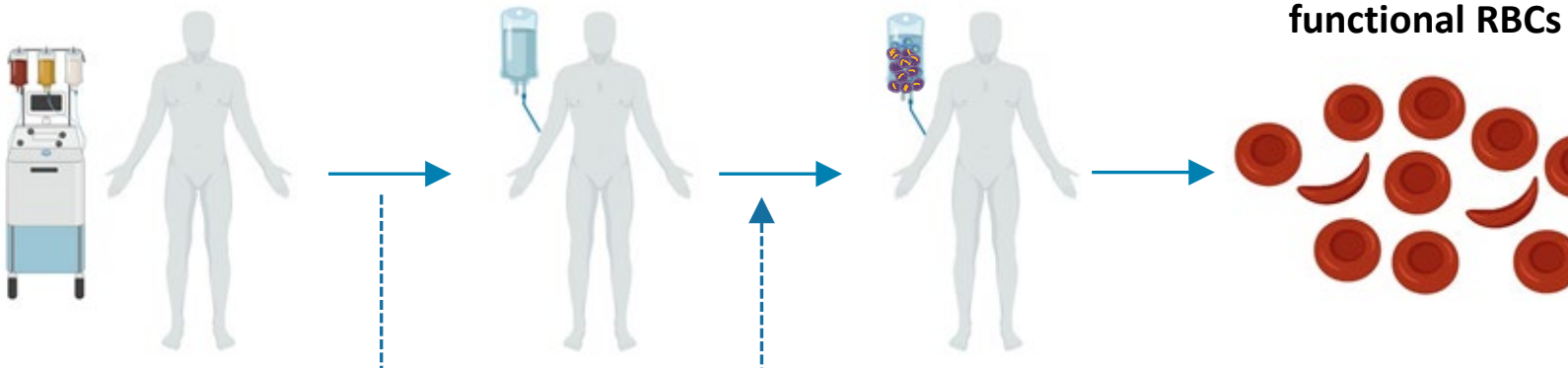
HSC collection
Mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

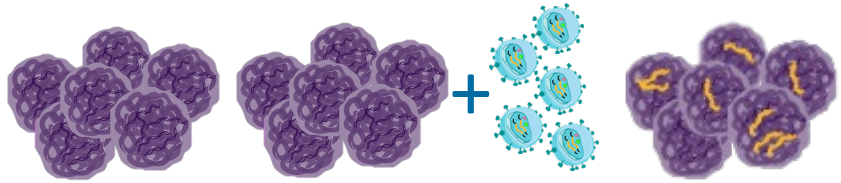
DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs

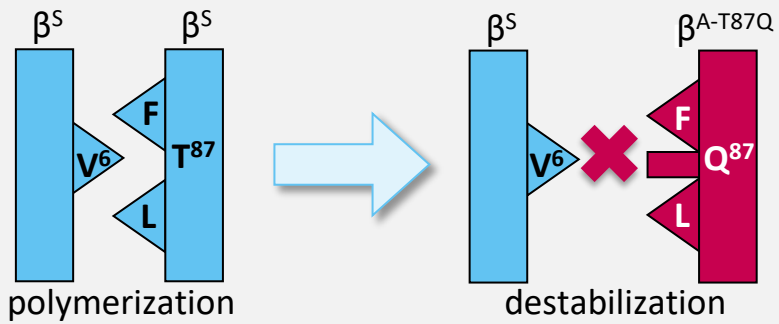
2-year follow-up → **Long-term follow-up study (NCT02633943)**



LentiGlobin DP centralized manufacturing



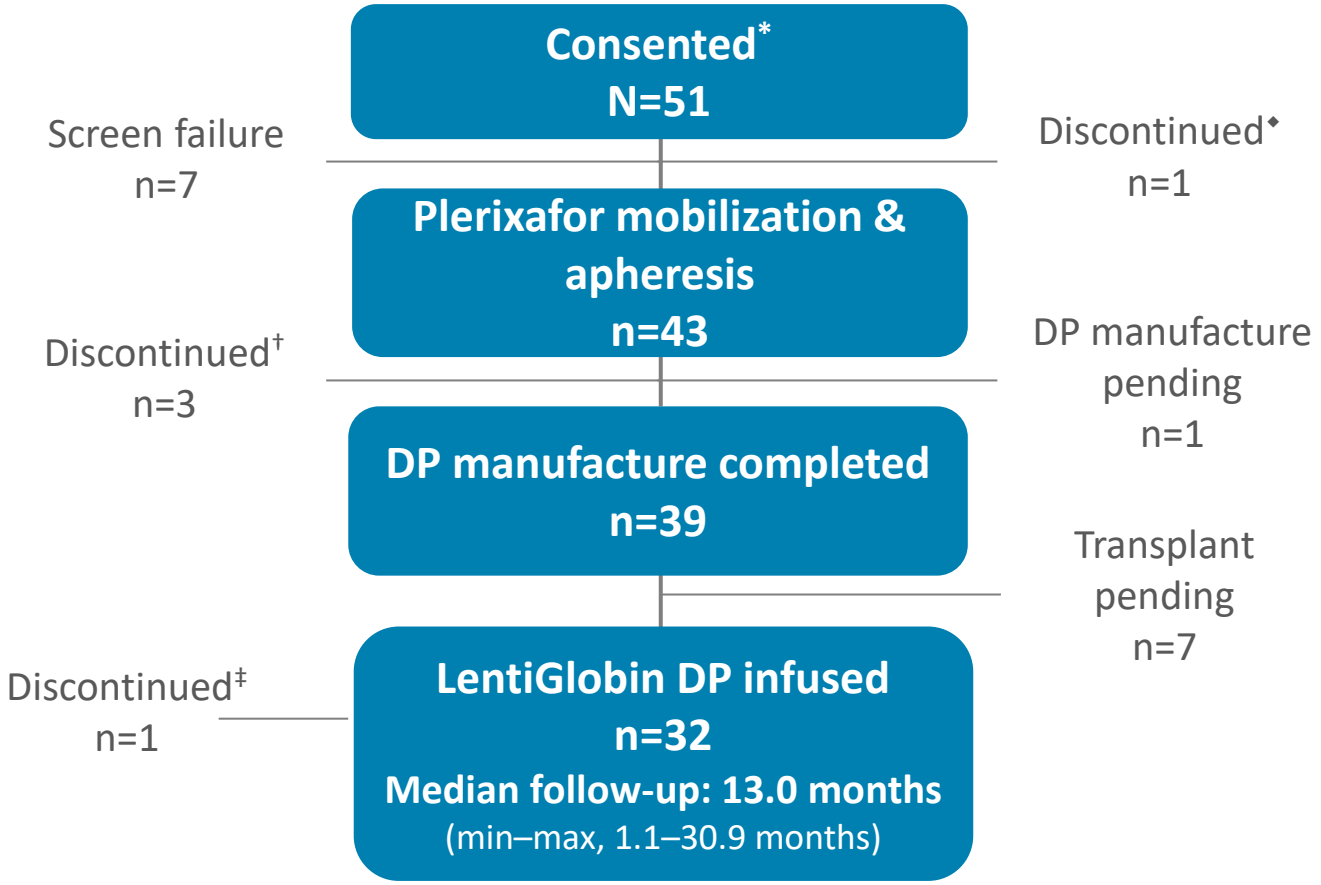
Select CD34+ cells | *Transduce with BB305 lentiviral vector* | *Cryopreserve, test, release DP*



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

DP, drug product; Hb, hemoglobin; HSCs, hematopoietic stem cells; RBCs, red blood cells SCD, sickle cell disease.

HGB-206 Group C: Study disposition



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

DP, drug product; max, maximum; min, minimum.

Data as of 20 August 2020

HGB-206 Group C: Patient characteristics for ITT population

N=43 Patients who started cell collection

Parameter	N=43
Age at consent, years, median (min–max)	**24** (12–38)
Age category 18–50 years, n 12– < 18 years, n	 **34** **9**
Gender, n	**18F 25M**
Genotype, n	**40** β^S/β^S **2** β^S/β^0 **1** β^S/β^+
SCD history	
Severe VOEs[*], n Annualized no. of events, median (min–max)	**39** **3.5** (0.5–16.0)
ACS, n Annualized no. of events, median (min–max)	**10** **0.5** (0.5–1)
Priapism, n	**2**
Any history of stroke, n	**6**

A severe VOE is as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or emergency room observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration

ACS, acute chest syndrome; F, female; ITT, intent to treat; M, male; max, maximum; min, minimum; no., number; SCD, sickle cell disease; sVOE, severe vaso-occlusive event.

Data as of 20 August 2020

HGB-206 Group C: Treatment and drug product characteristics

N=32 Infused Patients

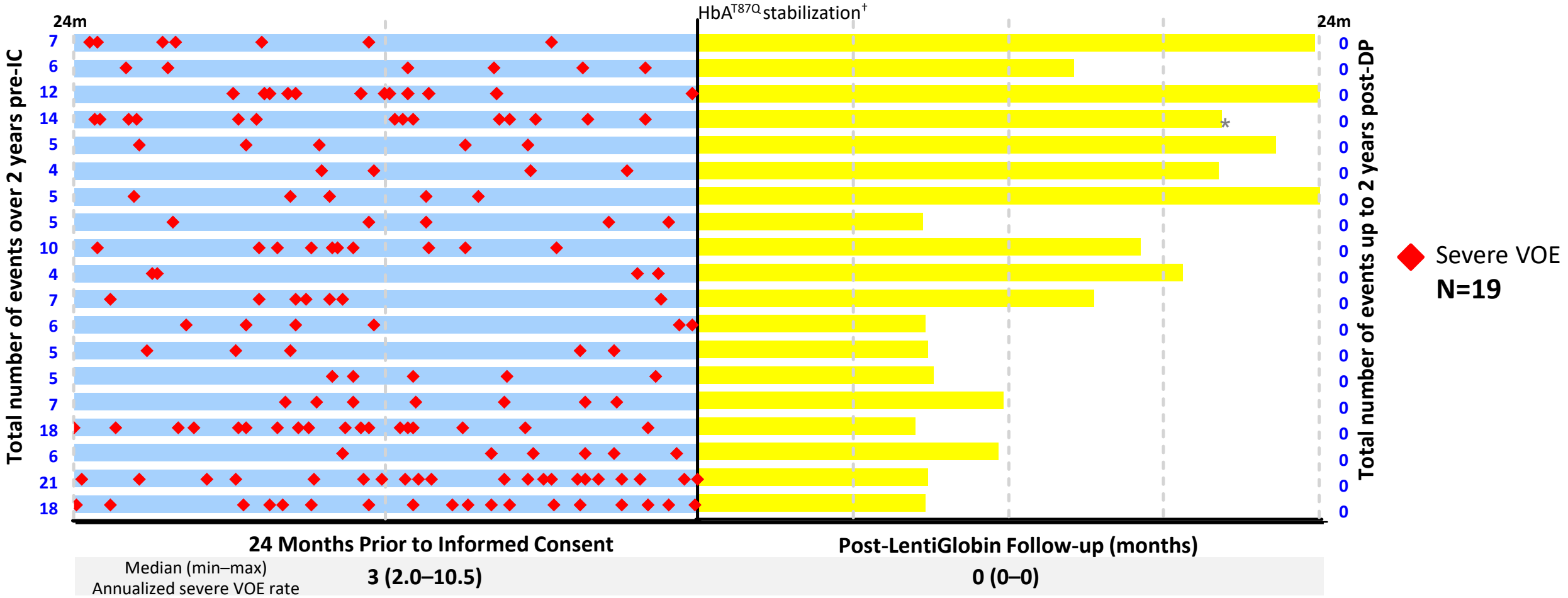
Parameter	N=32 Median (min–max)
Treatment characteristics	
No. of mobilization cycles	**2** (1–4)
CD34+ cells collected per mobilization cycle, x10^6 cells/kg	**10.4** (3.9–55.4)
Estimated average busulfan AUC, min*µmol[†]	**4843** (1445[⬥]–7322)
Neutrophil engraftment, ANC ≥ 500 /µl x 3 days, days	**19.5** (12–35)
Platelet engraftment, platelets > 50k /µl x 3 days, days[‡]	**30** (18–136)
Duration of hospitalization[§], days	**35** (26–65)
Drug product characteristics (per patient)	
Vector copy number, copies/diploid genome	**3.8** (2.3–5.7)
CD34+ cells transduced, %	**80.2** (63–93)
CD34+ cell dose, x10^6 cells/kg	**6.8** (3.0–24.0)

[†]5 patients pending AUC result; [⬥] Data error is being corrected; [‡]3 patients pending platelet engraftment at days 29, 30, and 39 post-DP infusion, but on their way to achieving engraftment; [§] Duration of hospitalization from conditioning to discharge.

ANC, absolute neutrophil count; AUC, area under the curve; DP, drug product; max, maximum; min, minimum; no., number.

Data as of 20 August 2020

HGB-206 Group C: Complete resolution of severe VOEs post-LentiGlobin treatment

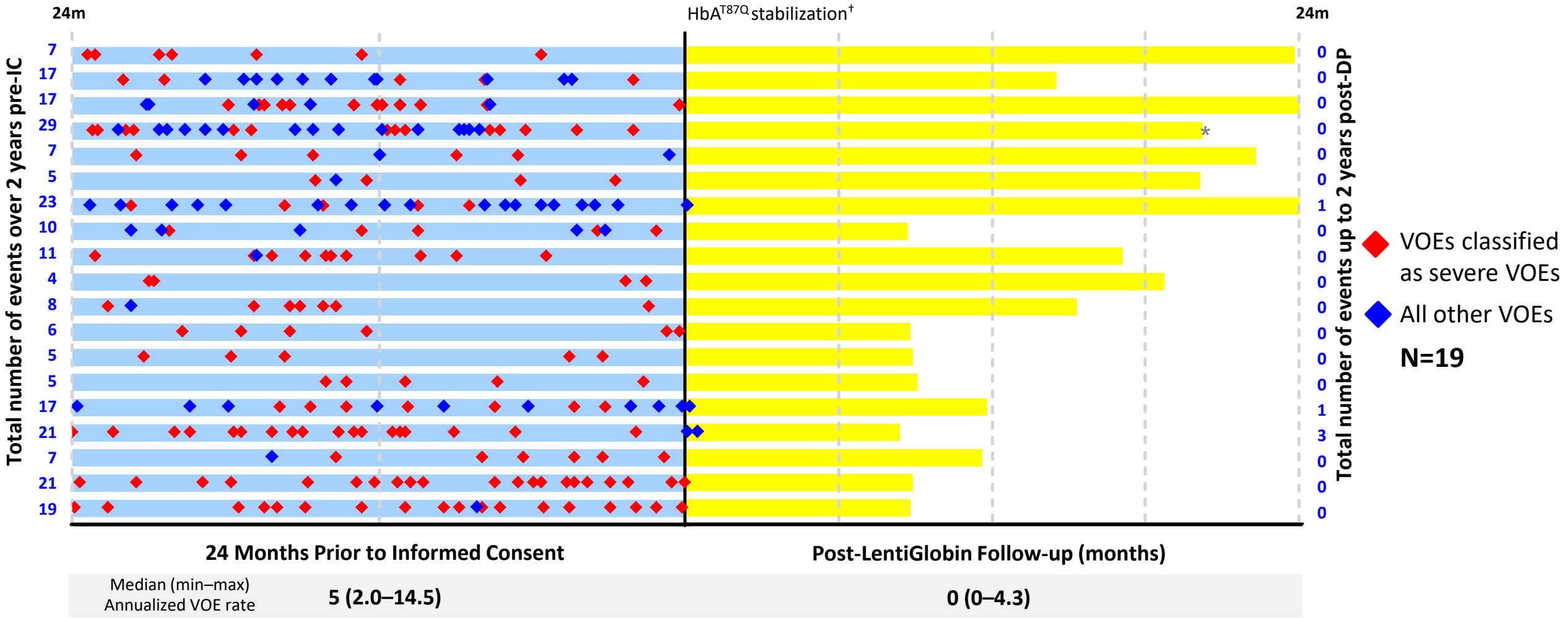


Protocol sVOEs are shown; Patients with ≥ 4 sVOE at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included. A severe VOE is as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or emergency room observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, acute splenic sequestration, and priapism; †HbA^{T87Q} expression stabilizes within 6 months; *One death, unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.
Note: In the last datacut, one patient had a non-serious VOC at Day 107. This event is recorded as an investigator reported sVOE but does not meet the definition of a protocol sVOE

DP, drug product; ER, emergency room; IC, informed consent; max, maximum; min, minimum; sVOEs, severe VOEs; VOE, vaso-occlusive event; VOC, vaso-occlusive crises.

Data as of 20 August 2020

HGB-206 Group C: Complete resolution of VOEs ≥6 months post-LentiGlobin treatment



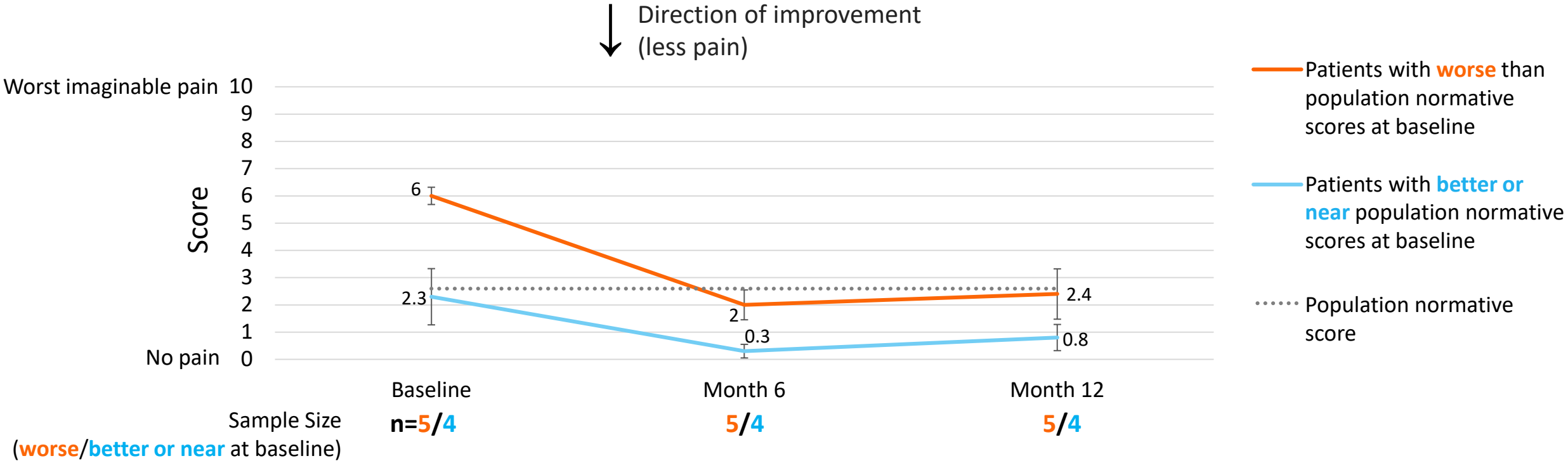
Protocol VOE are shown; Patients with ≥ 4 sVOE at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included. A VOE includes episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than 2 hours and severe enough to require care at a medical facility, a VOE includes acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration; †HbA^{T87Q} expression stabilizes within 6 months; *One death, unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.
Note: In the last datacut, one patient had a non-serious VOC at Day 107. The event is recorded as an investigator reported VOE but does not meet the definition of a protocol VOE

DP, drug product; IC, informed consent; max, maximum; min, minimum; sVOEs, severe VOEs; VOE, vaso-occlusive event; VOC, vaso-occlusive crisis.

Data as of 20 August 2020

HGB-206 Group C: Decrease in patient-reported pain intensity

PROMIS-57 Pain Intensity NRS



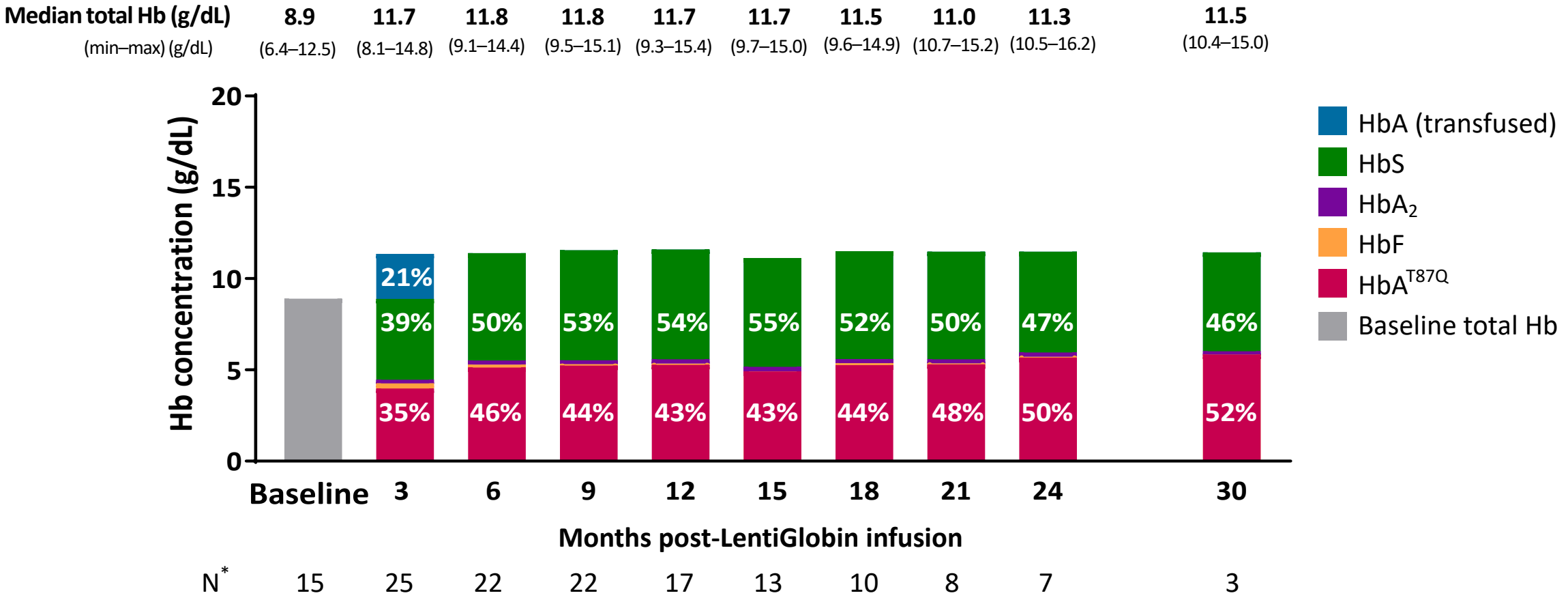
Patients with baseline values (n):	At Month 12
Worse than population normative values (n=5)	All 5 patients reported improvement, including clinically meaningful improvement in 4 patients
Better or near population normative values (n=4)	Patients either remained stable (n=2) or reported clinically meaningful improvement (n=2)

Average pain (0-10) over the past 7 days

NRS, Numeric Rating Scale; PROMIS, Patient Reported Outcomes Measurement Information System

Complete PROMIS-57 PRO data will be presented in abstract #365

HGB-206 Group C: Median HbA^{T87Q} ≥ 40% at ≥ 6 months post-LentiGlobin treatment



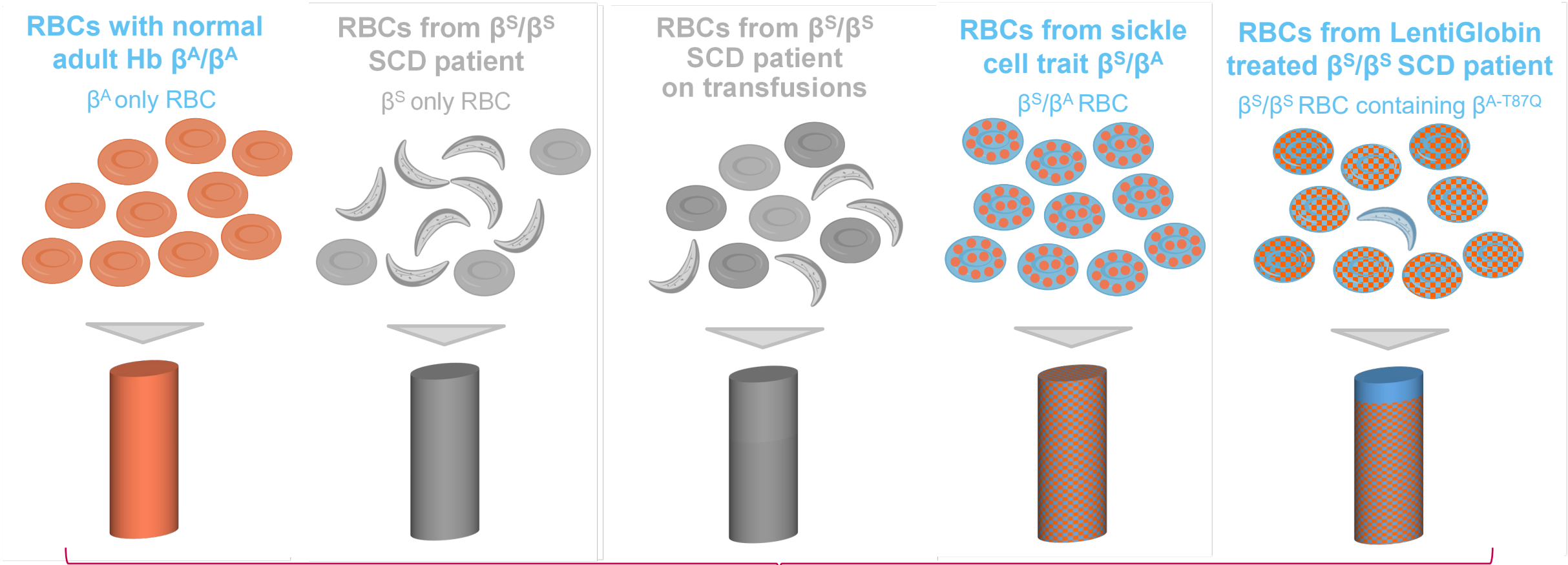
- In patients with ≥ 6 months of follow-up, median total Hb increased from 8.9 g/dL at baseline to ≥ 11.8 g/dL at Month 6
- At last visit in adolescents with ≥ 6 months of follow-up (n=6), median total Hb and HbA^{T87Q} were 13.5 g/dL and 6.1 g/dL, respectively

% represents median Hb fraction as % of total Hb; *Number of patients with data available. Hb, hemoglobin; max, maximum; min, minimum.

Data as of 20 August 2020

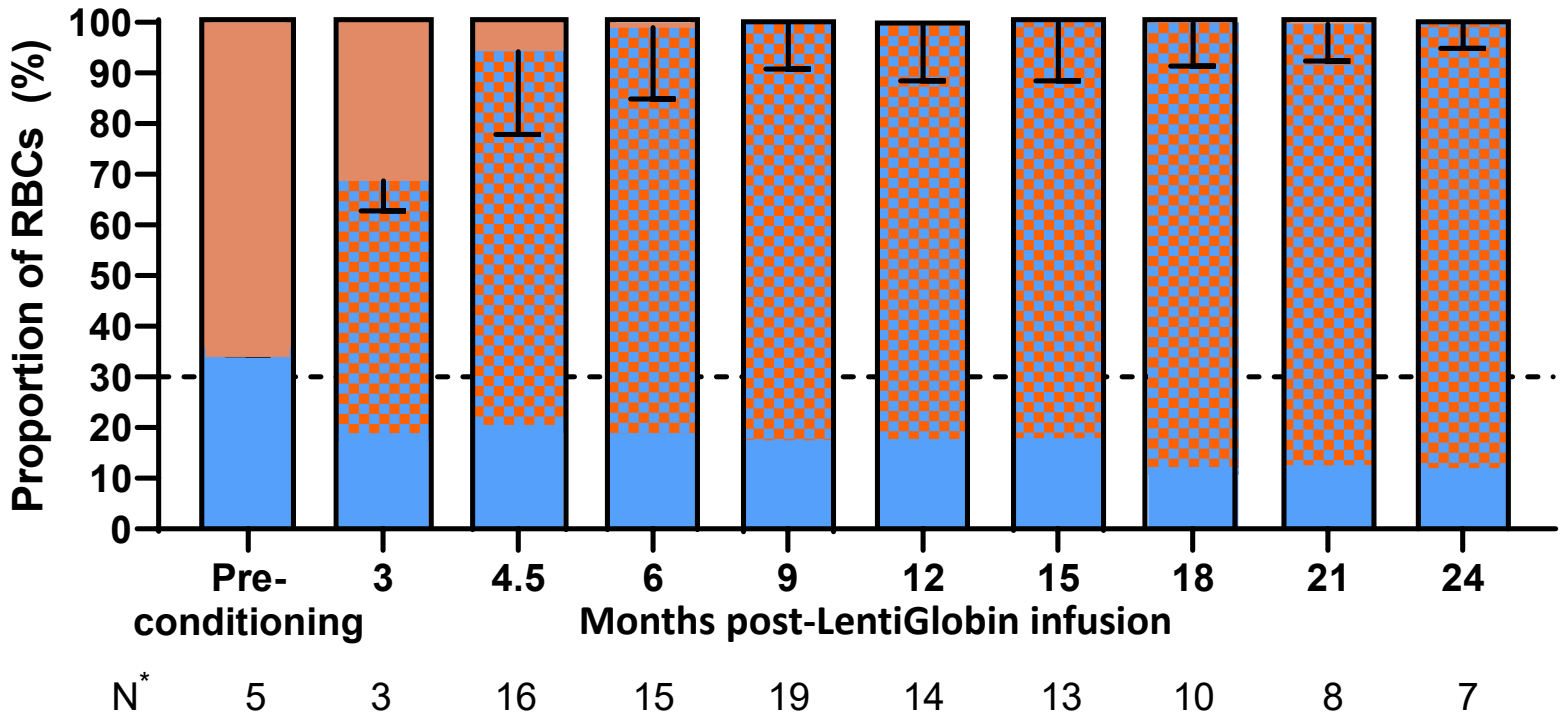
Exploratory assay allows for single-cell analysis of Hb expression

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



Hb, hemoglobin; RBCs, red blood cells; SCD, sickle cell disease.

HGB-206 Group C: Near pancellular expression of HbA^{T87Q} ≥ 6 months post-LentiGlobin treatment



RBCs with β^{A} only (Source: transfused blood)

RBCs positive for $\beta^{A\text{-}T87Q}$ by single cell Western (RBCs with detectable $\beta^{A\text{-}T87Q}$ in addition to β^{S})

RBCs with β^{S} only

- 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§

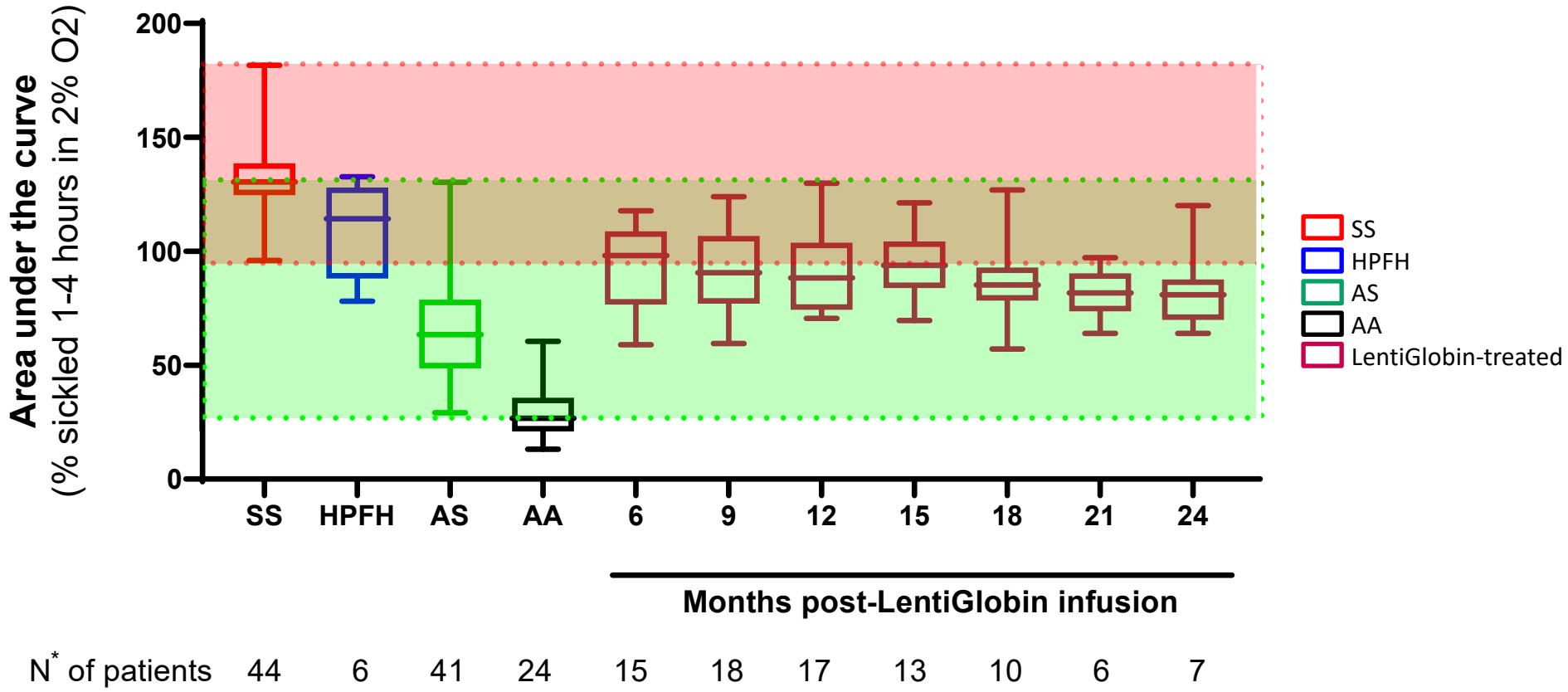
Mean & SD are depicted; Reducing HbS to < 30% is recommended by guidelines for exchange RBC transfusions for patients with SCD (indicated by dashed line); *Number of patients with data available; †Calculated as (% HbA^{T87Q} of total Hb/% RBCs containing $\beta^{A\text{-}T87Q}$) x MCH; ‡Calculated to 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; max, maximum; MCH, mean corpuscular hemoglobin; min, minimum; pg, picogram; RBCs, red blood cells; SD, standard deviation.

Data as of 20 August 2020

HGB-206 Group C: RBC propensity to sickle decreases over time post-LentiGlobin treatment

- An *ex-vivo* anti-sickling assay to study the impact of intracellular $\beta^{A\text{-}T87Q}$ and β^{S} levels on RBC sickling using flow cytometry



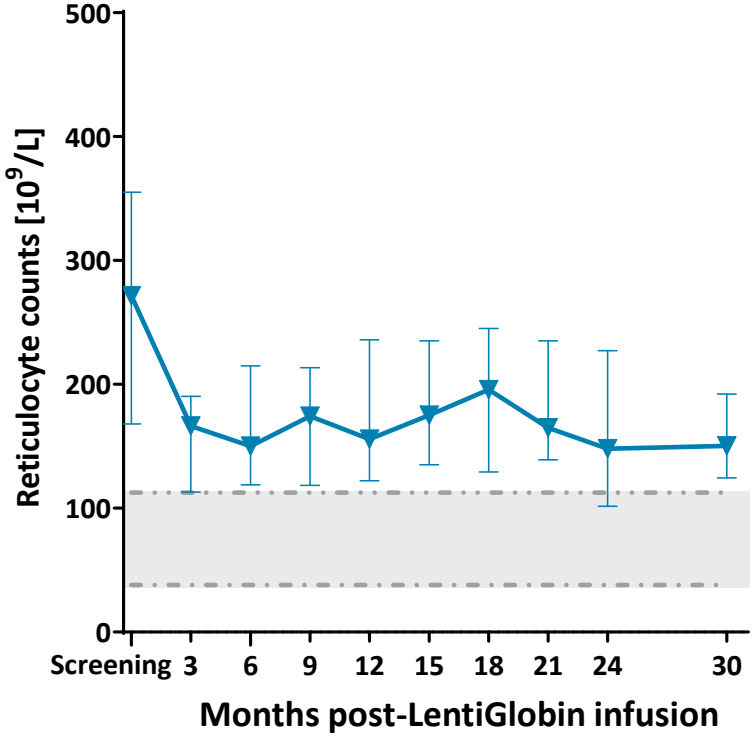
Red shaded area denotes range for patients with SS; green shaded area denotes range for patients with AS; line represents the median; limits are the min and max. *Number of patients with data available.

AA, both *HBB* alleles nonmutated; AS, sickle cell trait; HPFH, hereditary persistence of fetal hemoglobin; min, minimum; max, maximum; RBC, red blood cells; SS, sickle mutation on both *HBB* alleles.

Data as of 20 August 2020

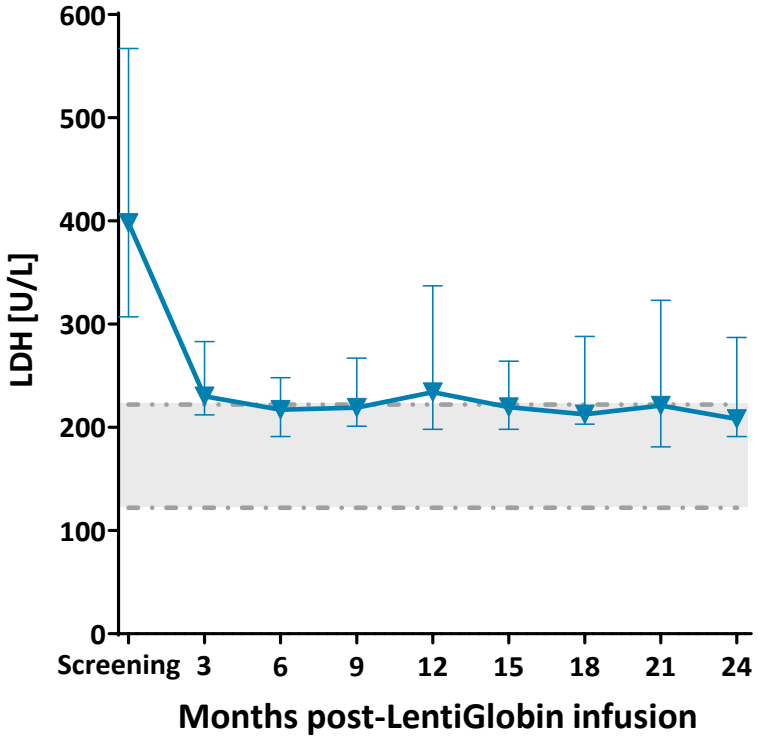
HGB-206 Group C: Hemolysis markers approaching near-normal levels post-LentiGlobin treatment

Reticulocyte counts



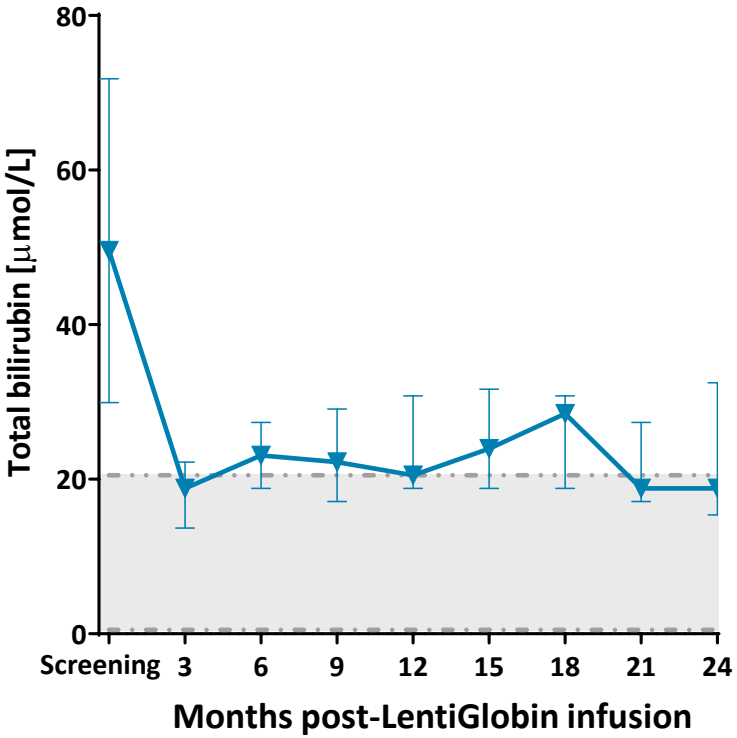
N*	31	26	23	22	17	14	10	9	7		3

Lactate dehydrogenase



N*	31	25	21	23	17	14	10	7	7

Total bilirubin



N*	32	26	24	23	17	14	10	9	7

Median (Q1, Q3) depicted; Dot-dash lines denote lower and upper limits of normal values; *Number of patients with data available; Q1, quartile 1; Q3, quartile 3.

Data as of 20 August 2020

HGB-206 Group C: Safety profile post-LentiGlobin treatment

Treatment-emergent ≥ Grade 3 AEs *Reported in ≥ 2 patients*[*]	**N=32** n (%)
Stomatitis	21 (65.6)
Febrile neutropenia	14 (43.8)
Increased ALT	4 (12.5)
Increased AST	4 (12.5)
Increased GGT	4 (12.5)
Increased blood bilirubin	2 (6.3)
Nausea	4 (12.5)
Premature menopause	2 (6.3)
Upper abdominal pain	2 (6.3)
Serious treatment-emergent AEs *Reported in ≥ 2 patients*	
Abdominal pain	2 (6.3)
Nausea	2 (6.3)
Drug withdrawal syndrome	2 (6.3)
Vomiting	2 (6.3)

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

- 1 patient with a nonserious Grade 2 DP-related AE[†]
- No cases of veno-occlusive liver disease
- No graft failure
- No vector-mediated RCL and no insertional oncogenesis
- One death, unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease
  - A 27-year-old patient with history of VOC/ACS (14 episodes/year), pulmonary hypertension, and venous thrombosis died following a cardiac arrest ~20 months post treatment
  - Autopsy showed cardiac biventricular dilation with concentric LVH and moderate cardiac interstitial fibrosis; there was no evidence of pulmonary embolism or stroke
  - Per PI, the patient appeared to have sudden death associated with cardiac fibrosis and other chronic organ injury

[†]1 patient with Grade 2 nonserious neutropenic fever on study day 10 (resolved on study day 18).

ACS, acute chest syndrome; AE, adverse event; DP, drug product; LVH, left ventricular hypertrophy; PIs, principal investigators; RCL, replication competent lentivirus; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Data as of 20 August 2020

HGB-206 Group C: Summary

- Complete resolution of severe VOEs with up to 24 months of follow-up
  - Complete resolution of VOEs after stabilization of HbA^{T87Q} expression[†], with up to 24 months of follow-up
- Decrease in patient-reported pain intensity over 12 months of follow-up
- Median total Hb is consistently ≥ 11 g/dL ≥ 6 months post-LentiGlobin treatment, with 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; reduction in RBC sickling propensity similar to patients with sickle cell trait
- Key markers of hemolysis approaching near-normal levels post-LentiGlobin treatment
- The safety profile post-LentiGlobin for SCD gene therapy remains generally consistent with myeloablative single-agent busulfan conditioning and underlying SCD

[†]HbA^{T87Q} expression stabilizes within 6 months.

Hb, hemoglobin; RBC, red blood cell; SCD, sickle cell disease; VOE, vaso-occlusive event.

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