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

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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

Enrollment Completed:
41 evaluable subjects†

Key Outcomes: Group C

- Weighted average of HbA^{T87Q} ≥ 30% of total Hb for ≥ 6 months post-DP
- Weighted average of total Hb increase ≥ 3 g/dL vs baseline OR total Hb ≥ 10 g/dL for ≥ 6 months post-DP
- A ≥ 75% reduction in severe VOEs in 24 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, hepatic sequestration, splenic sequestration, or priapism (priapism episodes considered if medical facility visit was needed). † 6 patients may not meet the severe VOE criteria but will be evaluated for globin response.
DP, drug product; Hb, hemoglobin; VOE, vaso-occlusive event

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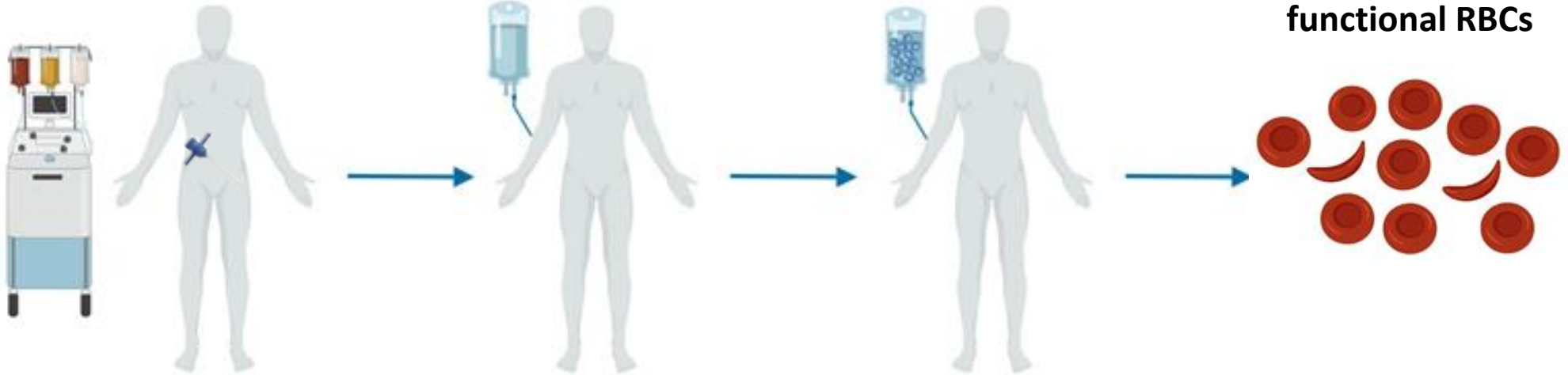
LentiGlobin gene therapy overview in patients with SCD

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



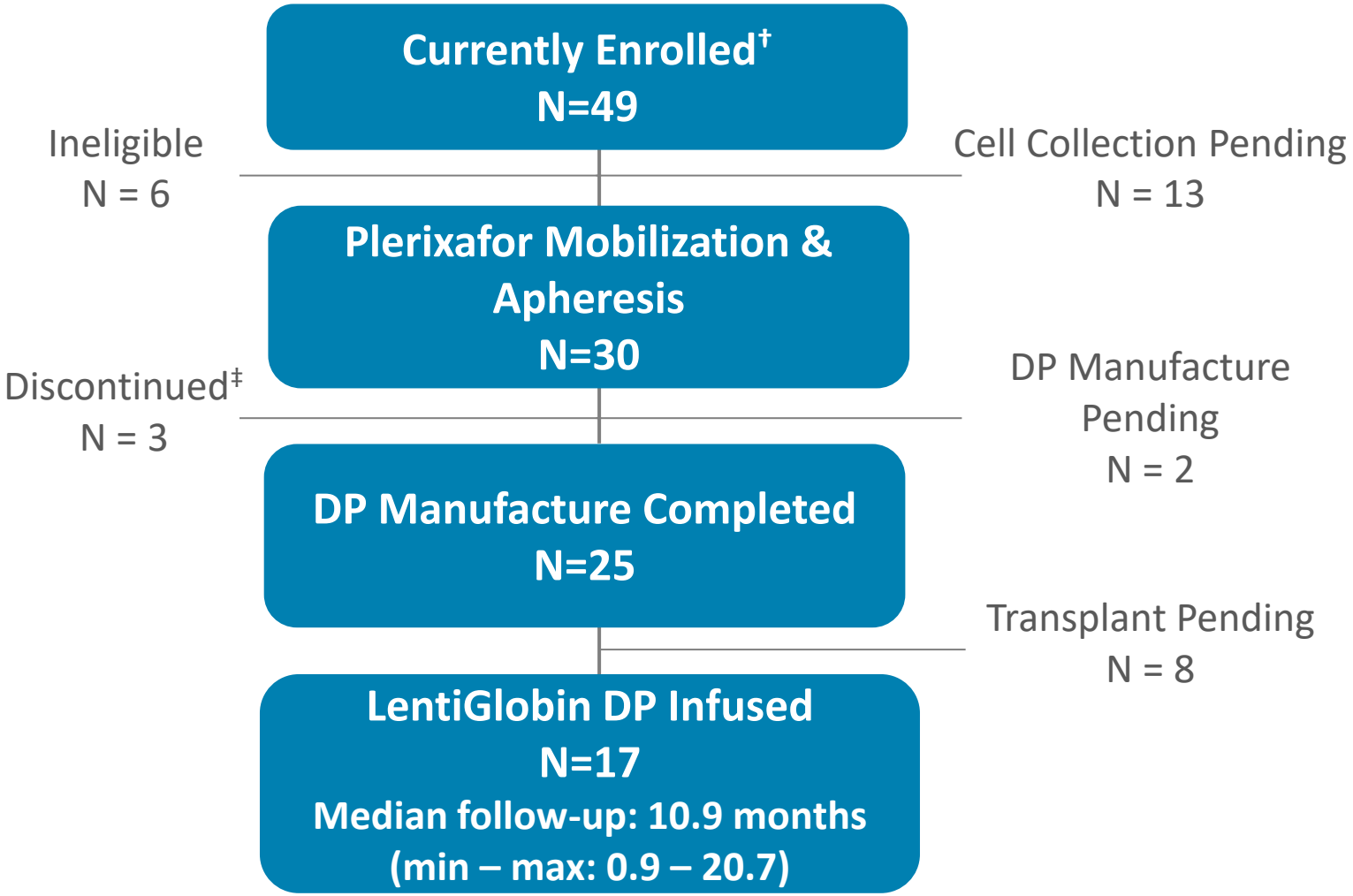
2-yr follow-up

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 Group C: Study Disposition



†Currently active, not recruiting
‡1 withdrew consent, 1 discontinued due to investigator discretion, 1 mobilization failure

HGB-206 Group C: Patient Characteristics for ITT Population

Parameter	N=30*
Age at consent, years median (min – max)	**25** (12 – 38)
Gender	**12F 18M**
Genotype, β^S/β^S	**29**[†]
SCD History	
VOCs[‡], n Annualized no. of events, median (min – max)	**25** **4.0** (2.0 – 15)
ACS[¥], n Annualized no. of events, median (min – max)	**2** **1** (1 – 1)
Any history of stroke, n	**6**
TRJV, n	**4**

*30 patients who started cell collection; [†]1 patient pending; [‡]≥ 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; ITT=intent to treat

HGB-206 Group C: Treatment and Drug Product Characteristics

Parameter	N=17* 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)
Average busulfan AUC, min*µmol/L	**4874** (4307 – 5182)
Follow-up, months	**10.9** (0.9 – 20.7)
Neutrophil engraftment, days (ANC ≥ 500 /µL)	**20** (15 – 26)
Platelet engraftment, days (platelets > 50k /µL)	**28** (17 – 136)
Duration of hospitalization, days	**36** (30 – 65)
Drug Product Characteristics	
Vector Copy Number	**3.6** (2.3 – 5.6)
% Transduced Cells	**80.2** (63 – 90)
CD34+ Cell Dose, x10^6 cells/kg	**6.3** (3.0 – 14.0)

*17 patients infused; ANC, absolute neutrophil count; AUC, area under the curve

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

Non-hematologic Grade ≥ 3 AEs *Post-DP infusion in ≥ 2 patients**	**N = 17 treated patients** n (%)
Febrile neutropenia	10 (58.8)
Stomatitis	9 (52.9)
Increased blood bilirubin	3 (17.6)
Upper abdominal pain	2 (11.8)
Increased alanine aminotransferase	2 (11.8)
Increased aspartate aminotransferase	2 (11.8)
Nausea	2 (11.8)
Premature menopause	2 (11.8)
Serious AEs *Post-DP infusion in ≥ 2 patients*	**N = 17 treated patients** n (%)
Nausea	2 (11.8)
Vomiting	2 (11.8)

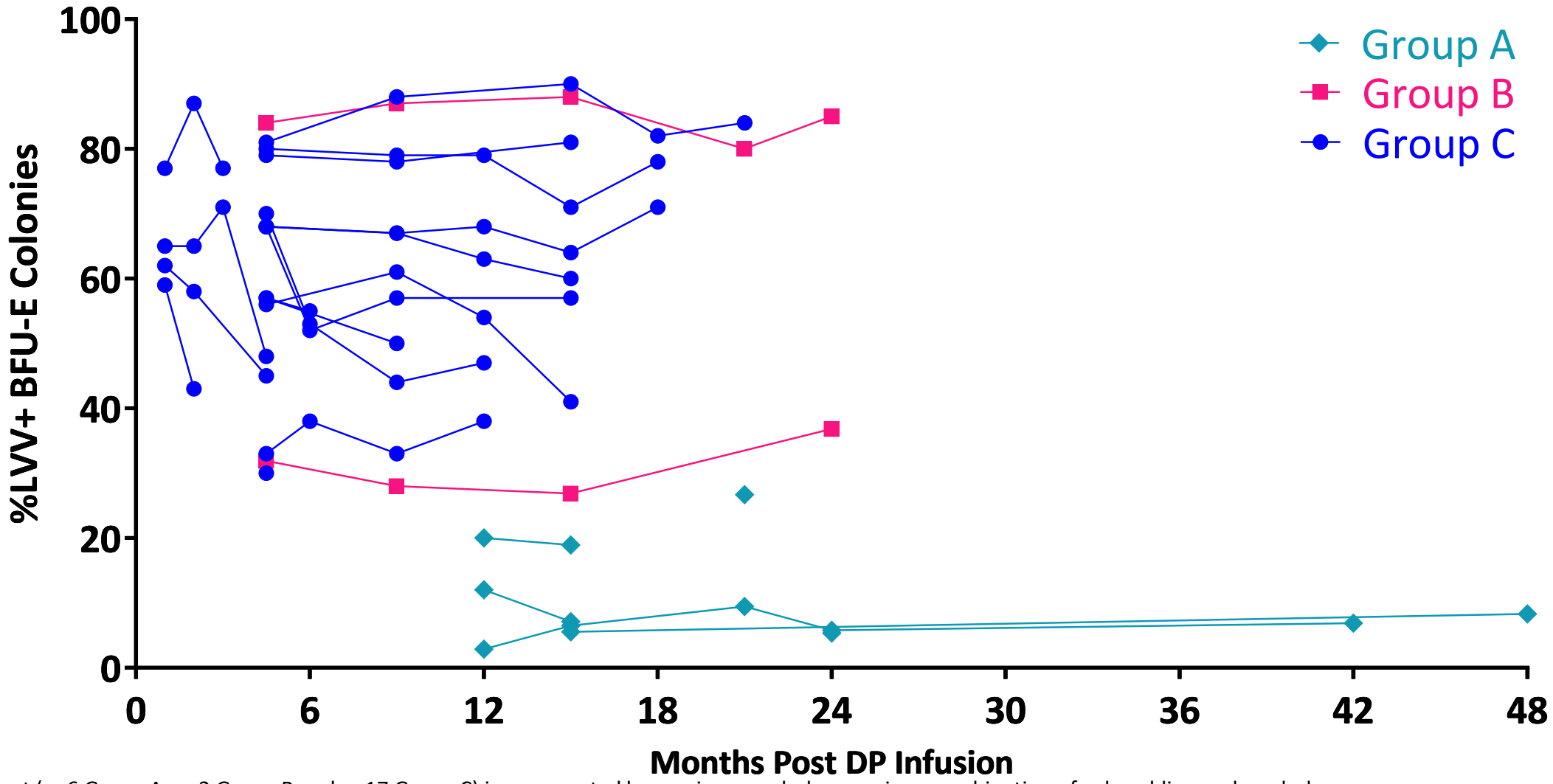
*Hematologic AEs commonly observed post-transplantation have been excluded

As of the last data cut date, 26 August 2019:

- 7/17 (41%) patients experienced ≥ 1 SAE
- 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

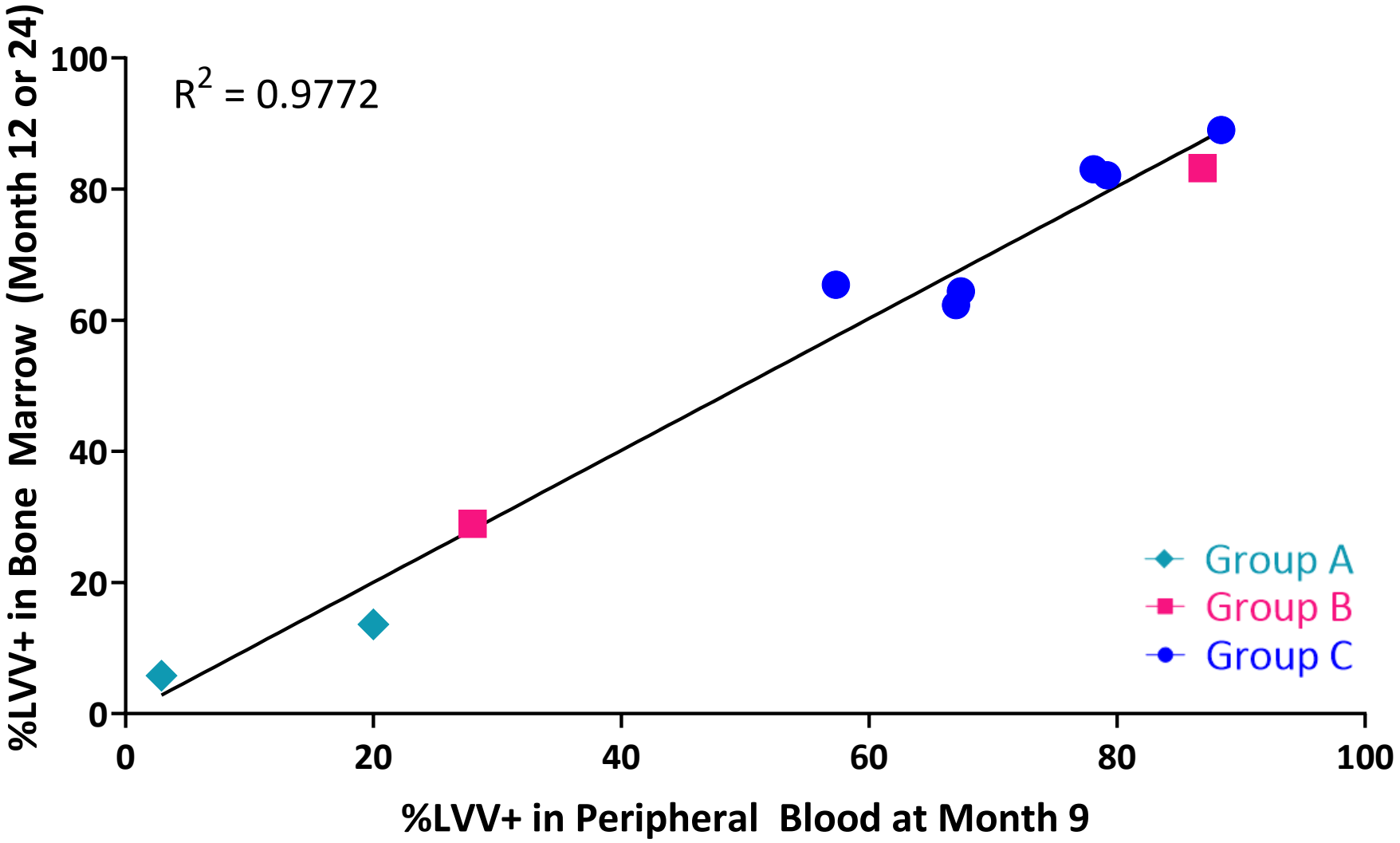
RCL, replication competent lentivirus

HGB-206: Refined Protocol Results in Higher %LVV+ in Peripheral Blood and LVV+ Cells Demonstrate Stable Engraftment



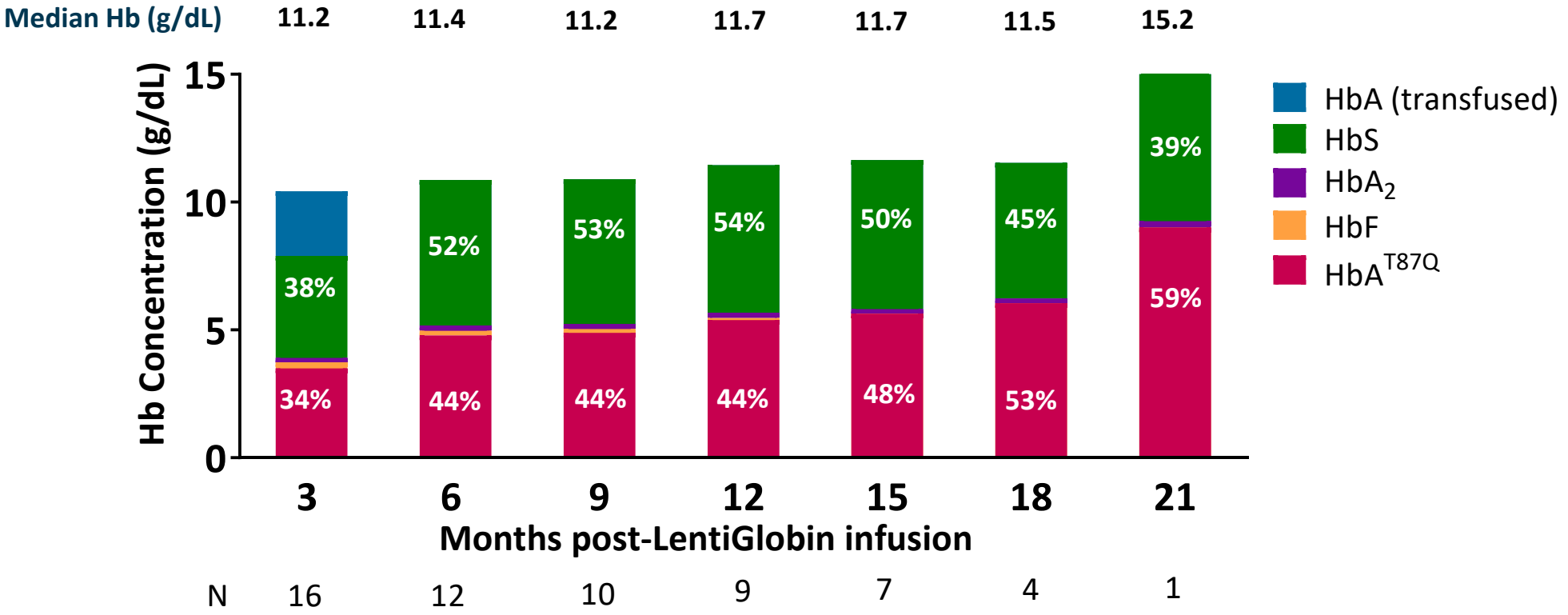
Each patient (n=6 Group A, n=2 Group B and n=17 Group C) is represented by a unique symbol or a unique combination of colored line and symbol
BFU-E, burst forming unit-erythroid; DP, drug product; LVV, lentiviral vector

HGB-206: %LVV+ in Peripheral Blood is a Good Proxy for Bone Marrow LVV-marking



BFU-E, burst forming unit-erythroid; BM, bone marrow; DP, drug product; Hb, hemoglobin; LVV, lentiviral vector; PB, peripheral blood

HGB-206 Group C: Hemoglobin Fractions Post-LentiGlobin Treatment

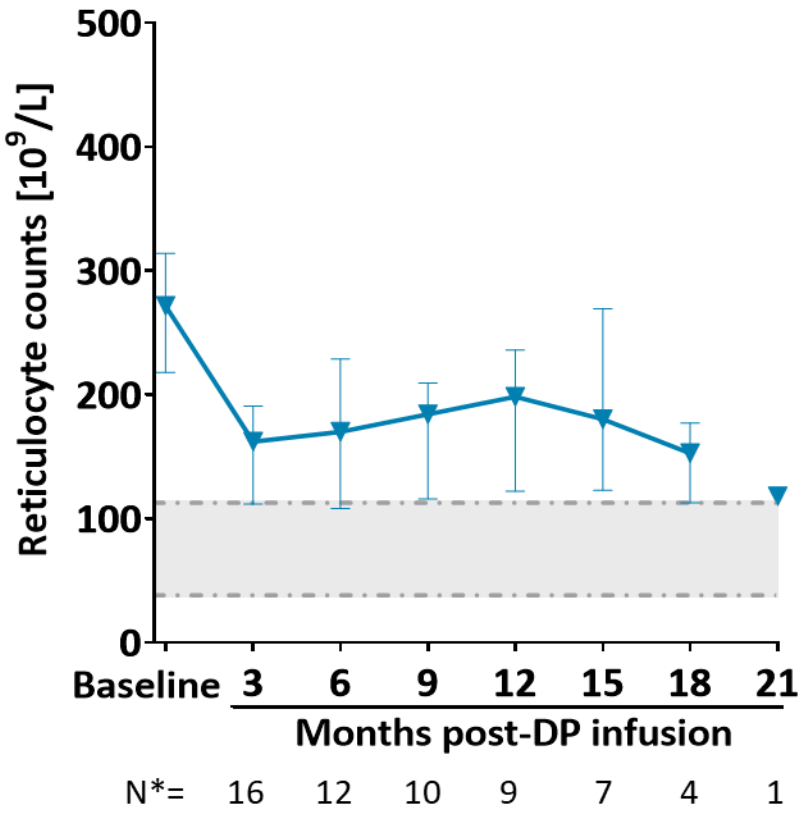


- Median HbS ≤ 60% at ≥ 6 months post-LentiGlobin treatment
- Median anti-sickling HbA^{T87Q} contribution is ≥ 40% at ≥ 6 months
- Total Hb and HbA^{T87Q} ranged from 9.3 – 15.2 g/dL and 2.7 – 9.0 g/dL, respectively, at last visit in patients with ≥ 6 months of follow-up

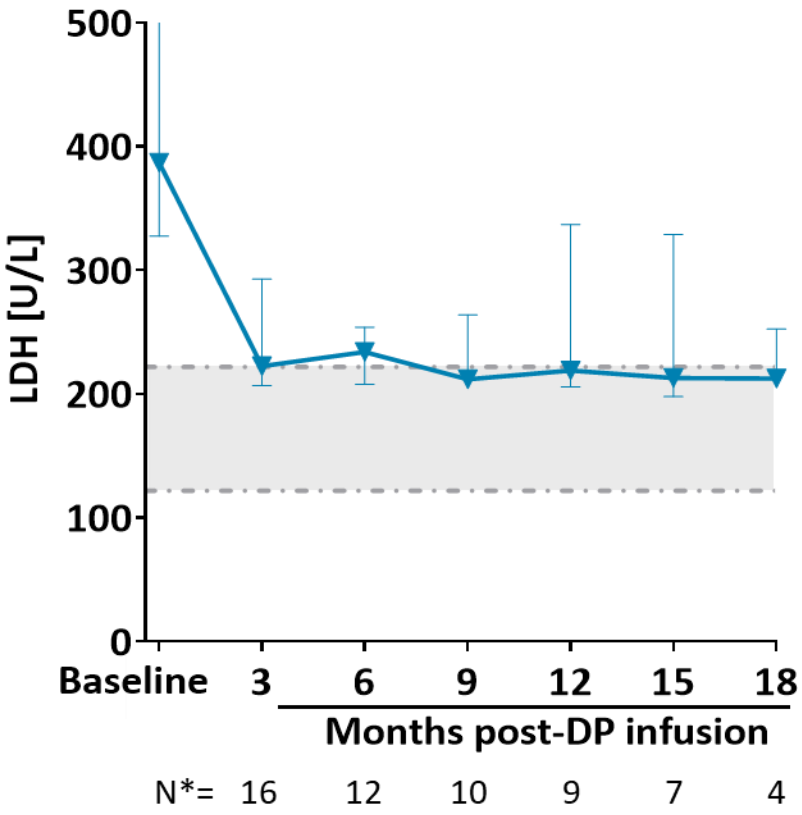
% represents median Hb fraction as % of total Hb; Hb, hemoglobin

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

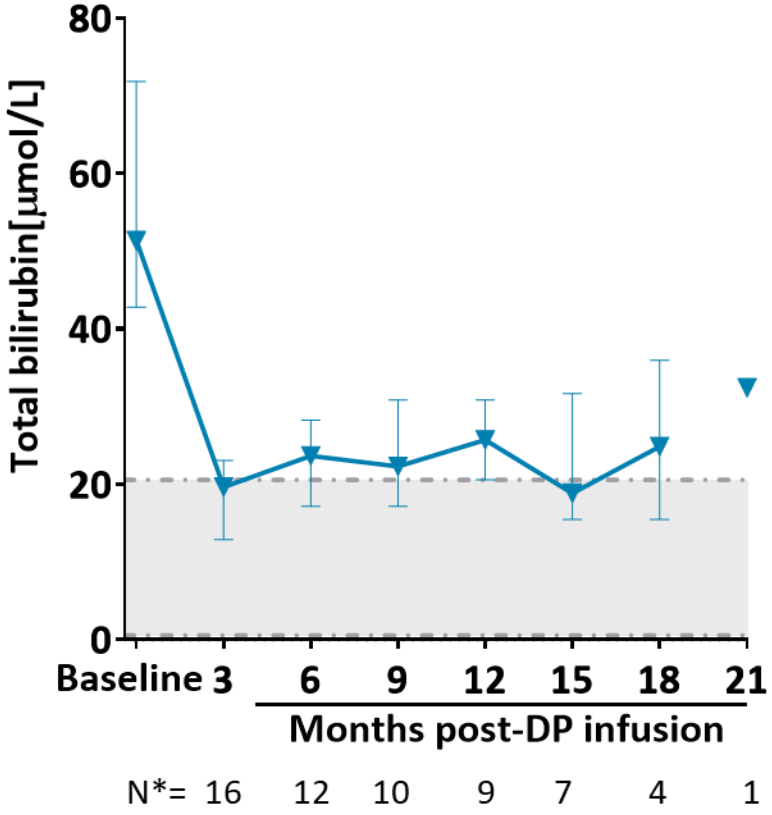
Reticulocyte Counts



Lactate Dehydrogenase



Total Bilirubin

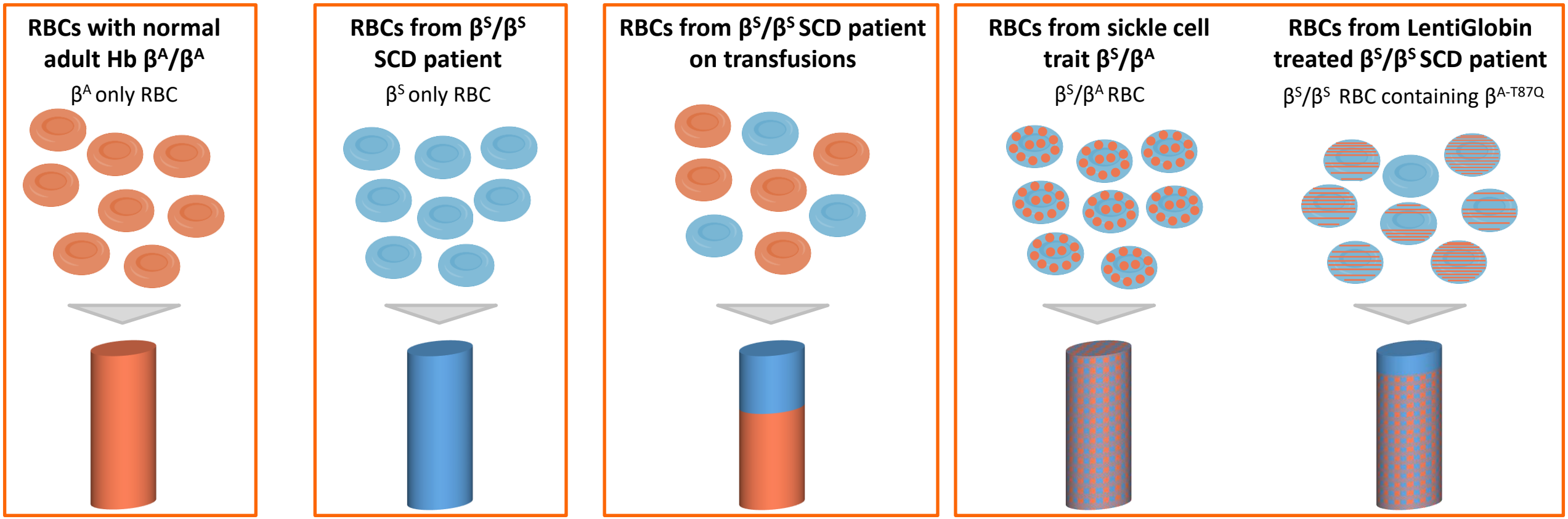


Hemolysis markers decreased post-LentiGlobin treatment

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

Pancellularity of HbA^{T87Q}: Exploratory assay allows for single-cell resolution of Hb expression

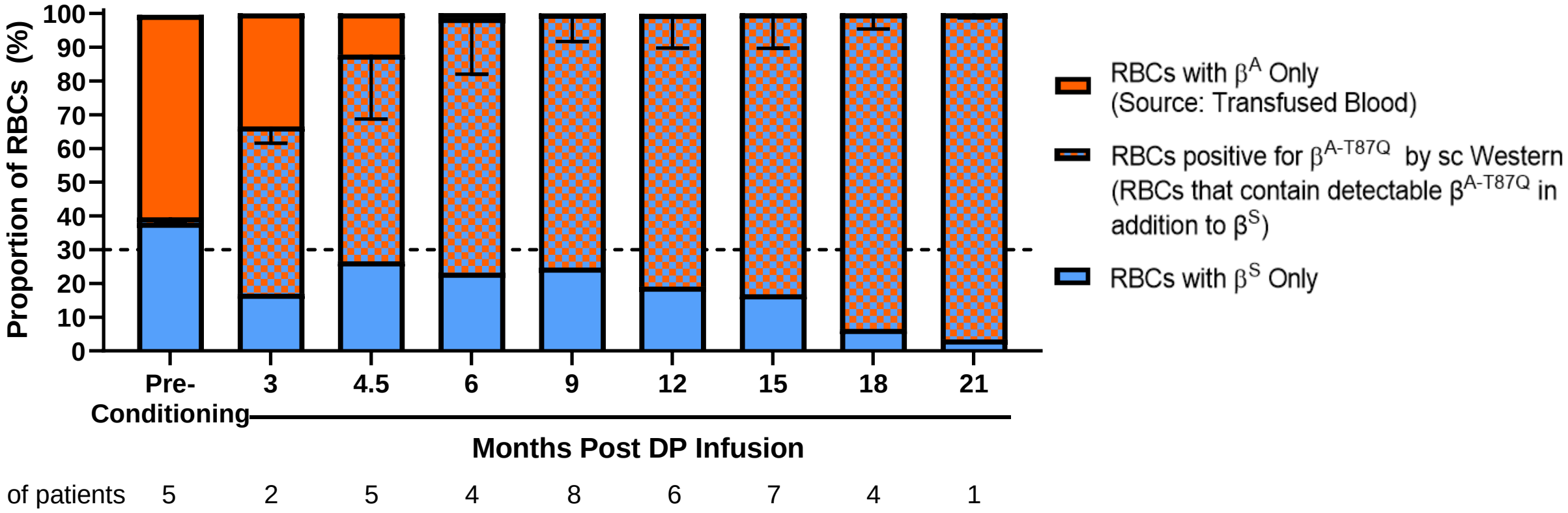
- Exploratory assay: Single red blood cell western with anti-β^S or anti-$\beta^A/\beta^{A\text{-}T87Q}$ antibodies



Hb, hemoglobin; RBC, red blood cells

On average, ≥ 80% of RBCs from patients treated with LentiGlobin contain $\beta^{A\text{-}T87Q}$ by Month 6

- Single RBC western assay was performed in multiple patient samples

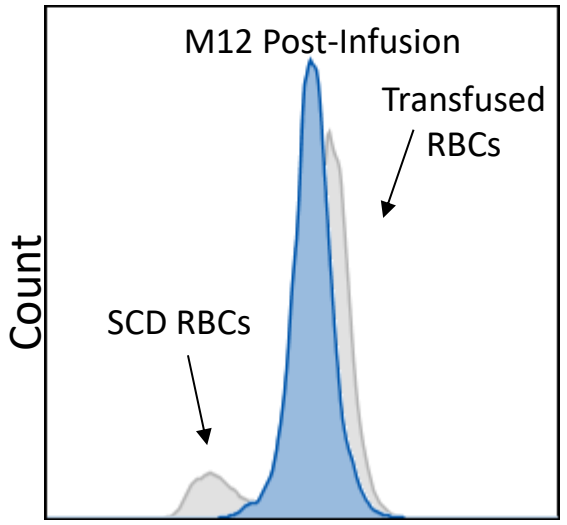


Mean ± SD is depicted - if N=1, data show technical replicates; *Pre-conditioning sample does not contain any $\beta^{A\text{-}T87Q}$, signal is due to error rate of multiples

RBCs, red blood cells; SD, standard deviation

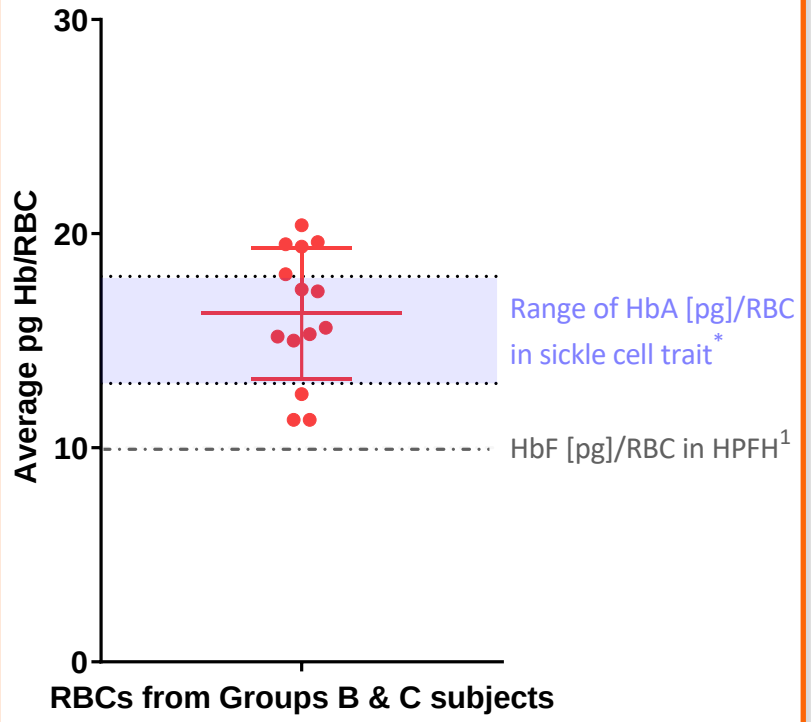
Combination of outputs from multiple assays allows quantifying average amount of HbA^{T87Q} per RBC

Uniform distribution of $\beta^{A\text{-}T87Q}$



Average pg Hb/RBC =
(% HbA^{T87Q} of total Hb/
% RBCs containing $\beta^{A\text{-}T87Q}$) x MCH

HbA^{T87Q} pg/RBC comparable to trait pg HbA /RBC & HPFH pg HbF/RBC

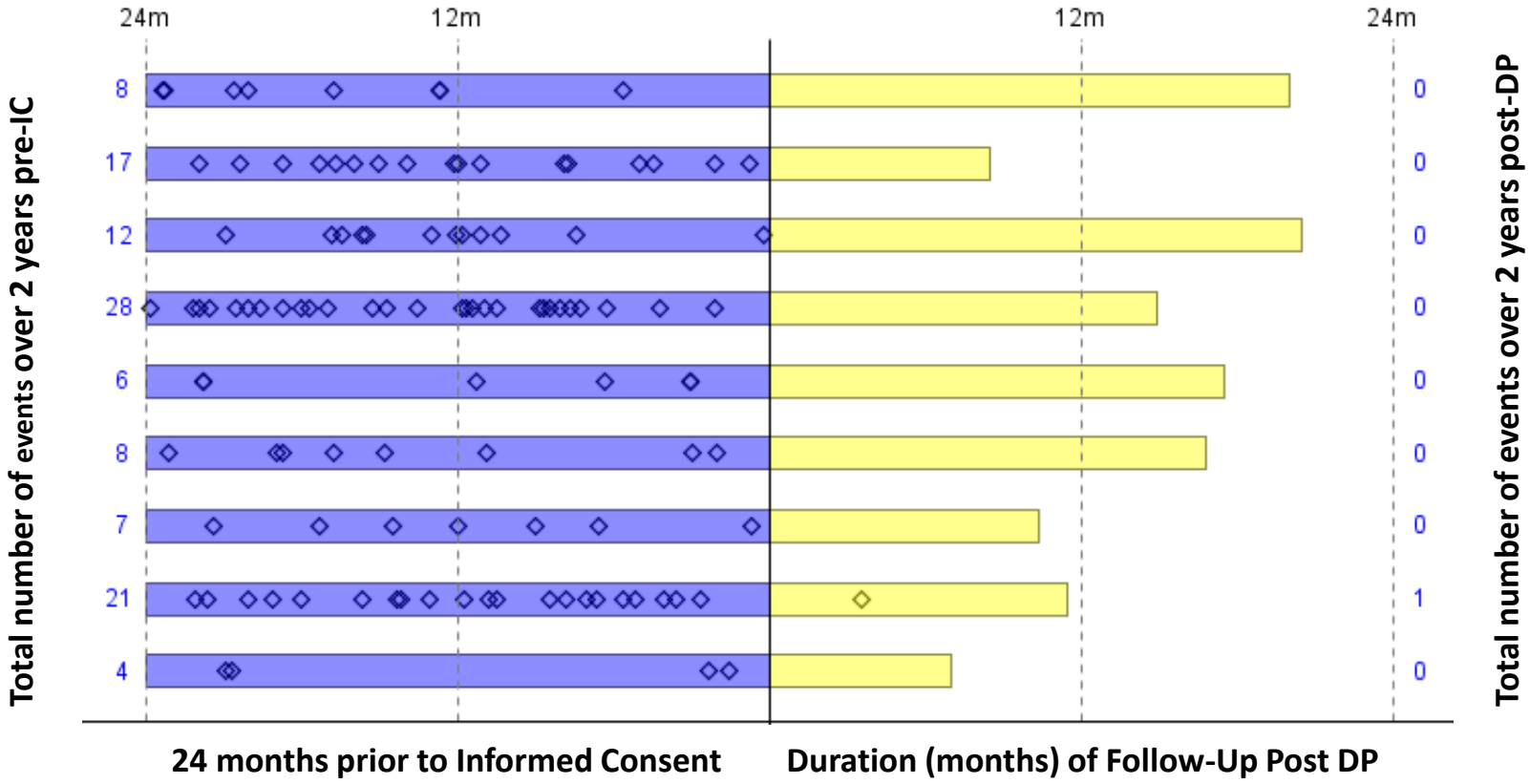


*Calculated using 50% HbA/RBC for the lower end of the range and 60% HbA/RBC for the upper end of the range

1. Steinberg MH et al., Blood. 2014;123(4):481-5.

DP, drug product; HPFH, hereditary persistence of fetal hemoglobin; MCH, mean corpuscular hemoglobin; RBC, red blood cells

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



- The reduction of annualized rate is 99% [95% confidence interval, 92.5 – 100%]
- No ACS or serious VOCs occurred in any Group C patient post-LentiGlobin treatment to date (between 1-21 months follow-up)
- As previously reported, 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
IC, informed consent

HGB-206 Group C: Summary

- The safety profile post-LentiGlobin for SCD gene therapy is generally consistent with that of myeloablative single-agent busulfan conditioning
- No ACS or serious VOCs were observed in Group C patients with 1 to 21 months follow-up post-DP
- Median HbS levels were ≤ 60% at ≥ 6 months post-LentiGlobin treatment, with a median anti-sickling HbA^{T87Q} contribution ≥ 40%
- Median total unsupported Hb was ≥ 10 g/dL at last visit in patients with ≥ 6 months of follow-up
- Treatment with LentiGlobin decreased key markers of hemolysis
- Stable LentiGlobin engraftment in peripheral blood ≥ ~4.5 months post DP infusion
  - Peripheral blood can serve as proxy for assessment of gene marking in bone marrow
- Longer follow-up for durability and safety in this study, and data from additional studies, will help further assess the clinical impact of LentiGlobin for SCD

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

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