Current Results of LentiGlobin Gene Therapy in Patients with Severe Sickle Cell Disease Treated Under a Refined Protocol in the Phase 1 HGB-206 Study

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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

Target enrollment: up to 29

Study Objectives

- Primary objective: Safety
- Key Secondary Objectives:
  - Frequency of VOCs and ACS
  - HbA^{T87Q} production
  - Total Hb and Hb fractions
  - Vector copies in peripheral blood

Study initiated August 2014

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

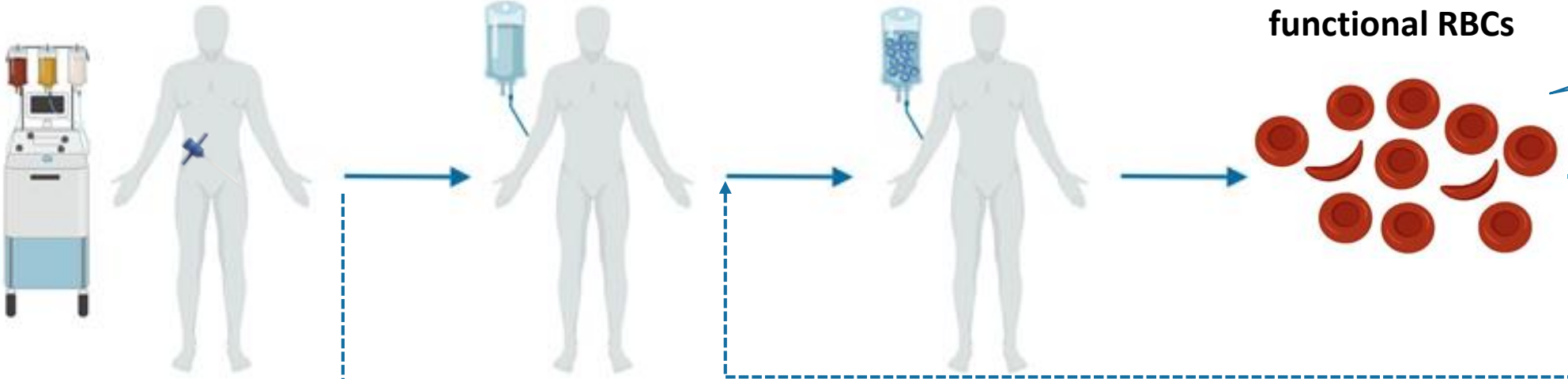
LentiGlobin gene therapy overview in patients with SCD

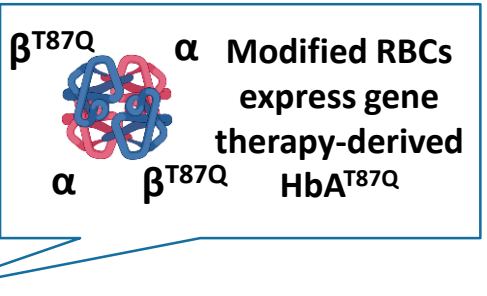
HSC collection
Bone marrow harvest or mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs



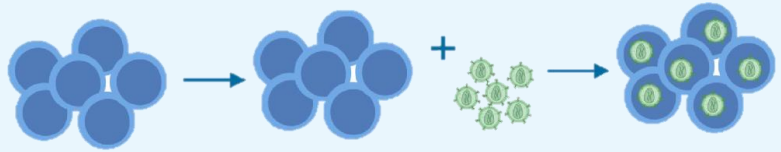


2-yr follow-up

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

LentiGlobin DP centralized manufacturing

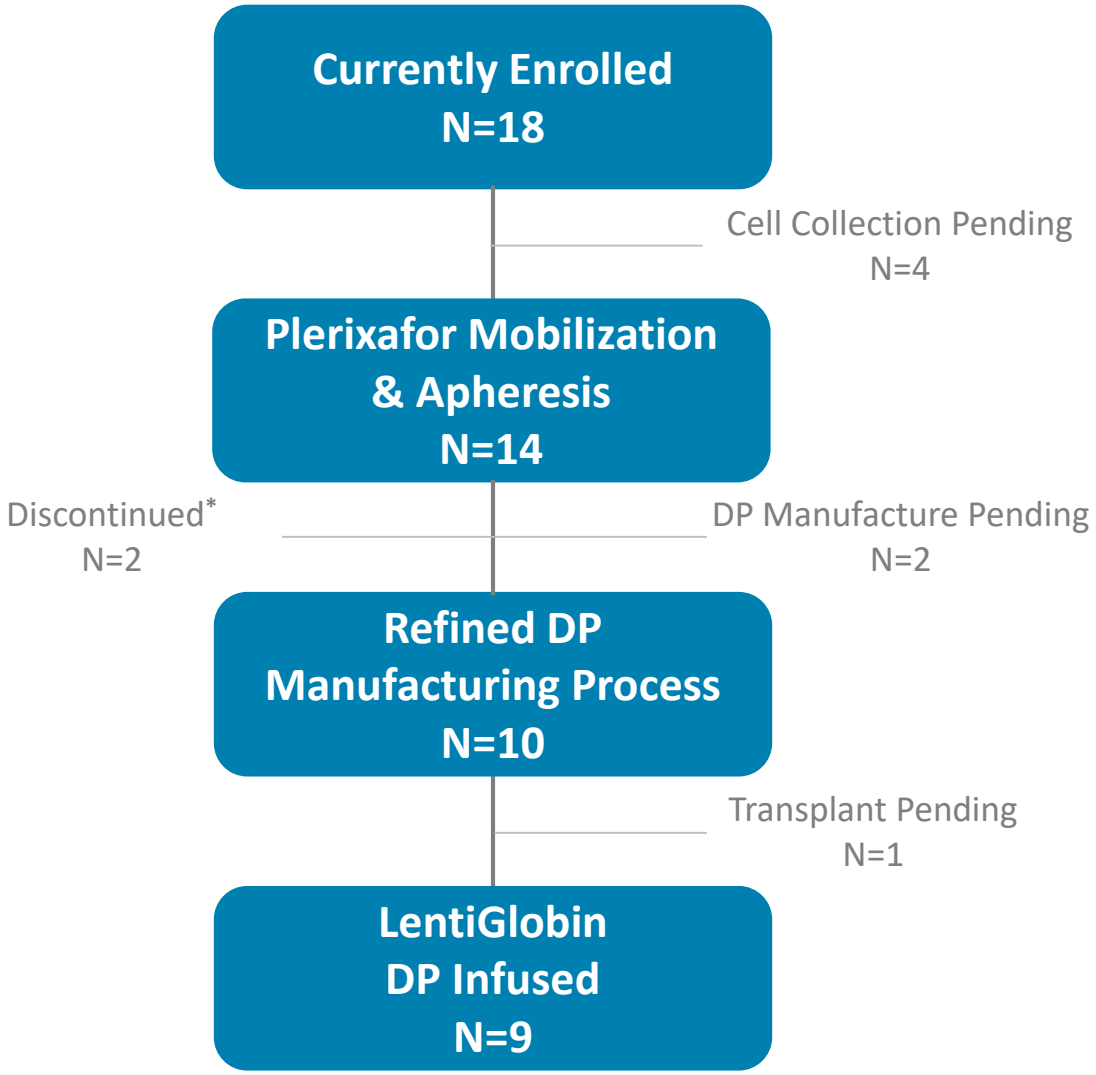


Select CD34+ cells → *Transduce with BB305 lentiviral vector* → *Cryopreserve, test, release DP*

DP, drug product; HSCs, hematopoietic stem cells, PB, peripheral blood; RBC, red blood cell

HGB-206 Group C: Disposition

Currently enrolling



*1 withdrew consent, 1 discontinued due to adverse event; DP, drug product

HGB-206 Group C: Patient characteristics

N=14 patients who started cell collection

Parameter	Group C N=14
Age at consent, years median (min – max)	**25.5** (18 – 36)
Gender	**6 F 8 M**
Genotype, β^S/β^S	**14**
SCD History	
Hydroxyurea, n	**8**
VOCs[*], n Annualized no. of events, median (min – max)	**9** **6.5** (3.5 – 14.0)
ACS[†], n Annualized no. of events, median (min – max)	**2** **1** (1 – 1)
Stroke, n	**3**
TRJV > 2.5 m/s, n	**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 Group C: Treatment characteristics

N=9 infused patients

Parameter	Group C N=9 Median (min – max)
No. of mobilization cycles	**2** (1 – 3)
No. of apheresis procedures per mobilization cycle	**2** (1 – 2)
CD34+ cells collected per mobilization cycle, x10^6 cells/kg	**8.9** (2.4 – 21.6)
Busulfan AUC[†], µM*min	**4787** (4608 – 5182)
Follow-up, months	**5.2** (0.5 – 9.2)
Neutrophil engraftment[‡], days	**19.5** (18 – 24)^
Platelet engraftment[#], days	**28** (12 – 136)¶
Duration of hospitalization[§], days	**36** (30 – 65)^

[†]Estimated average daily busulfan exposure over 4 days; [‡]Absolute neutrophil count [ANC] ≥ 500 cells/µL for 3 consecutive days; [#]Unsupported platelet count ≥ 50,000/µL for 3 consecutive measures; [§]Initiation of hospitalization from conditioning to discharge post drug product infusion; ^Based on data for 8 patients; ¶Based on data for 7 patients

- 7 patients had platelet engraftment (≥ 50,000/µL) by data cut-off, 6 in ≤ 90 days

HGB-206 Group C: Improved safety profile with plerixafor mobilization/apheresis vs BMH

- **In 35 apheresis procedures in 14 patients, 5 grade ≥ 3 AEs were reported in 3 patients**

Grade ≥ 3 AEs in 14 patients who had plerixafor mobilizations / apheresis	N=14 n (%)
Vaso-occlusive pain[1]	2 (14)
Abdominal pain	1 (7)
Hypomagnesaemia	1 (7)
Non-cardiac chest pain	1 (7)

[1] Were considered serious and consistent with patients' histories of VOEs. Patients were hospitalized, or hospitalization was prolonged for standard management. Both patients recovered without sequelae.

- **In 26 BMHs in 11 patients,* 18 grade ≥ 3 AEs were reported in 6 patients†**

*9 Group A and 2 Group B; †Patient could have experienced same AE more than once

AE, adverse event; BMH, bone marrow harvest; VOE, vaso-occlusive event

HGB-206 Group C: Safety profile consistent with myeloablative busulfan conditioning

Non-hematologic grade ≥ 3 AEs* *Post DP infusion in ≥ 2 patients*	**N=9 n (%)**
Febrile neutropenia	6 (67)
Stomatitis	6 (67)
Serious AEs* *Post DP infusion in ≥ 1 patient*	**N=9 n (%)**
Abdominal pain	1 (11)
Depression	1 (11)
Drug withdrawal syndrome	1 (11)
Hallucination	1 (11)
Mucosal inflammation	1 (11)
Nausea	1 (11)
Non-cardiac chest pain	1 (11)
Splenic hematoma	1 (11)
Vomiting	1 (11)

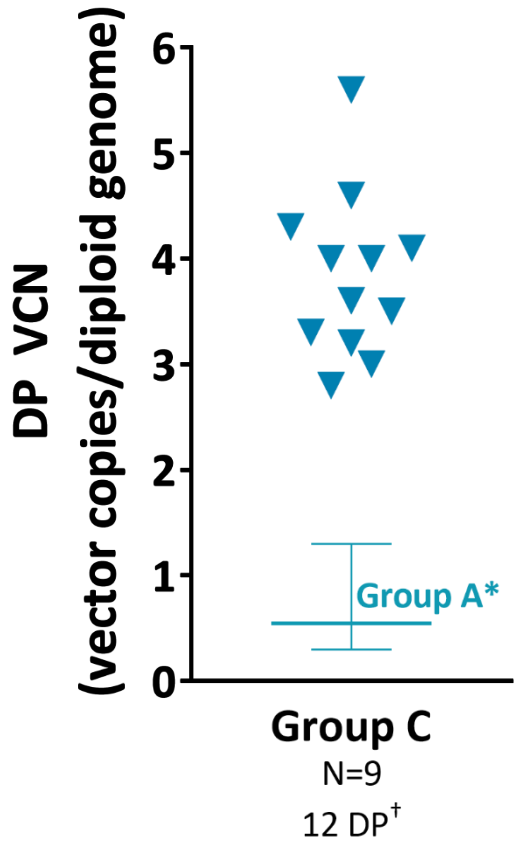
*Hematologic AEs commonly observed post-transplant have been excluded

- **No VOEs observed post DP infusion**
- **No AE considered related to LentiGlobin**
- **Serious AEs were reported in 4 patients**
- **No cases of VOD observed to date**
- **No graft failure or deaths reported**
- **No vector-mediated RCL detected to date**
- Early data suggest no clonal dominance - Integration site (IS) analyses available for two patients at 6-month visit
  - Total IS: 18,829 and 9,266; most frequent clone frequency: 0.4% and 0.8%

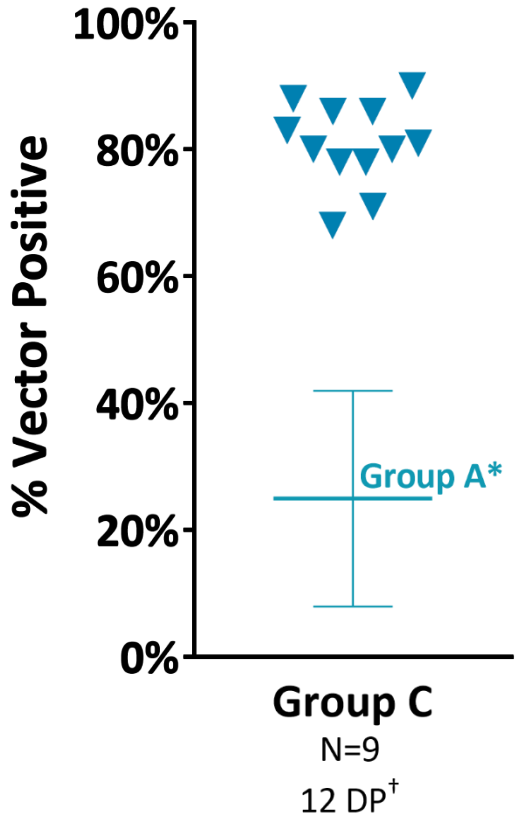
AE, adverse event; DP, drug product; RCL, replication competent lentivirus; VOD, veno-occlusive liver disease; VOE, vaso-occlusive event

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

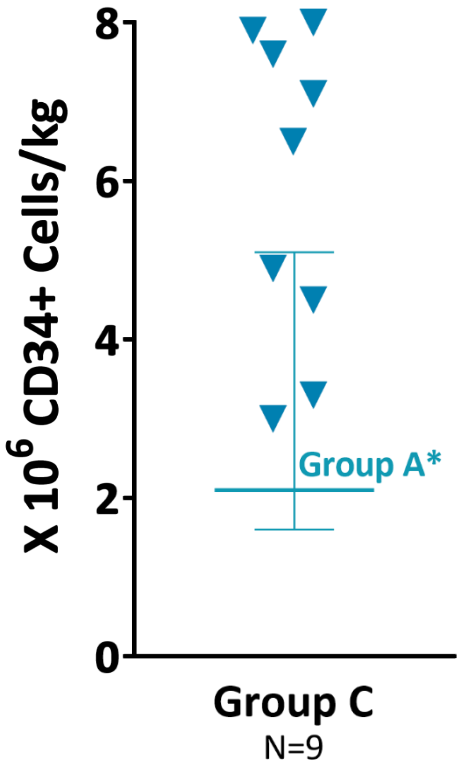
Vector copy number



% Transduced cells



CD34+ cell dose



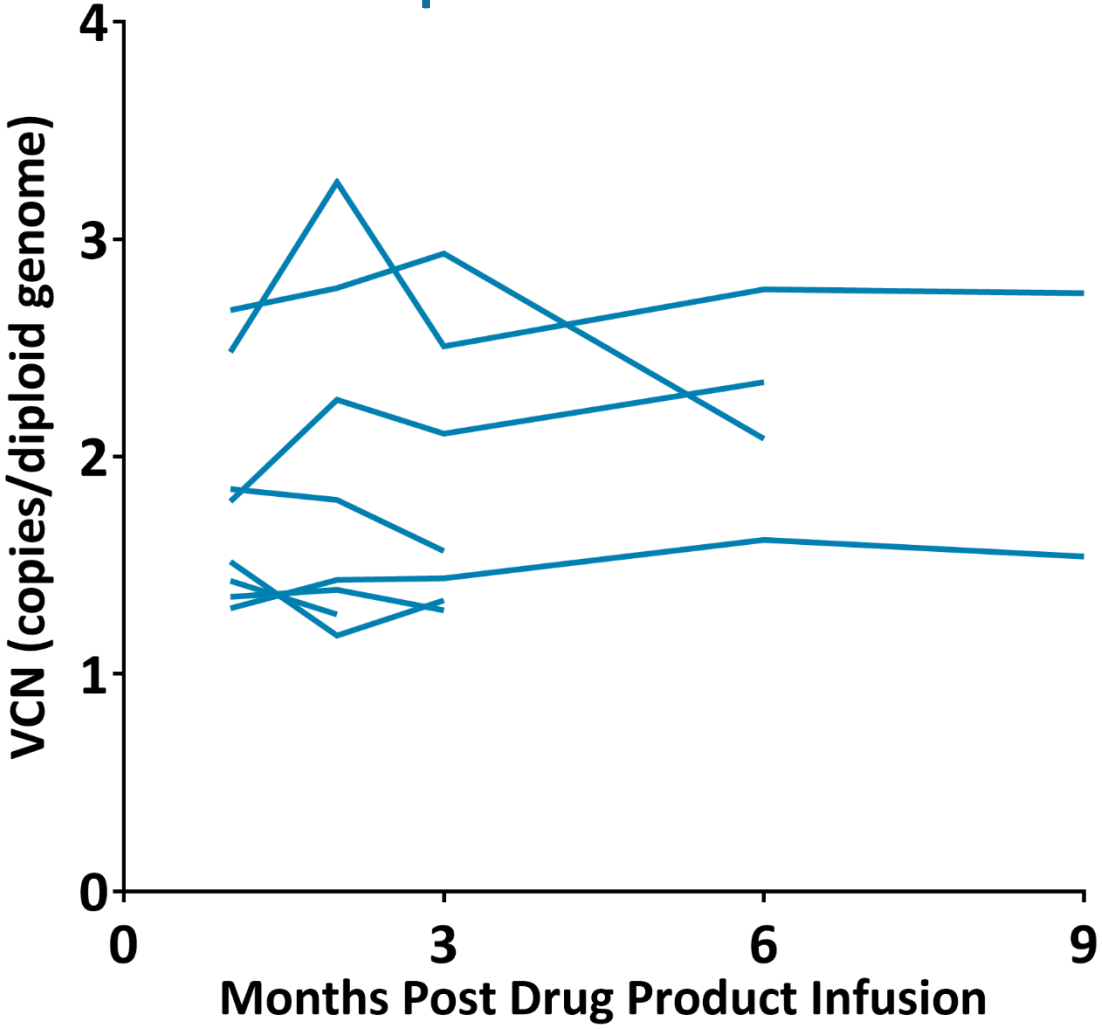
	Vector copy number	% Transduced cells	CD34+ cell dose
Median (min – max)	**3.8 (2.8 – 5.6)**	**81 (68 – 90)**	**6.5 (3.0 – 8.0)**

*Group A shown as median (min – max); †Number of DP exceeds number of patients since some patients were harvested or mobilized more than once

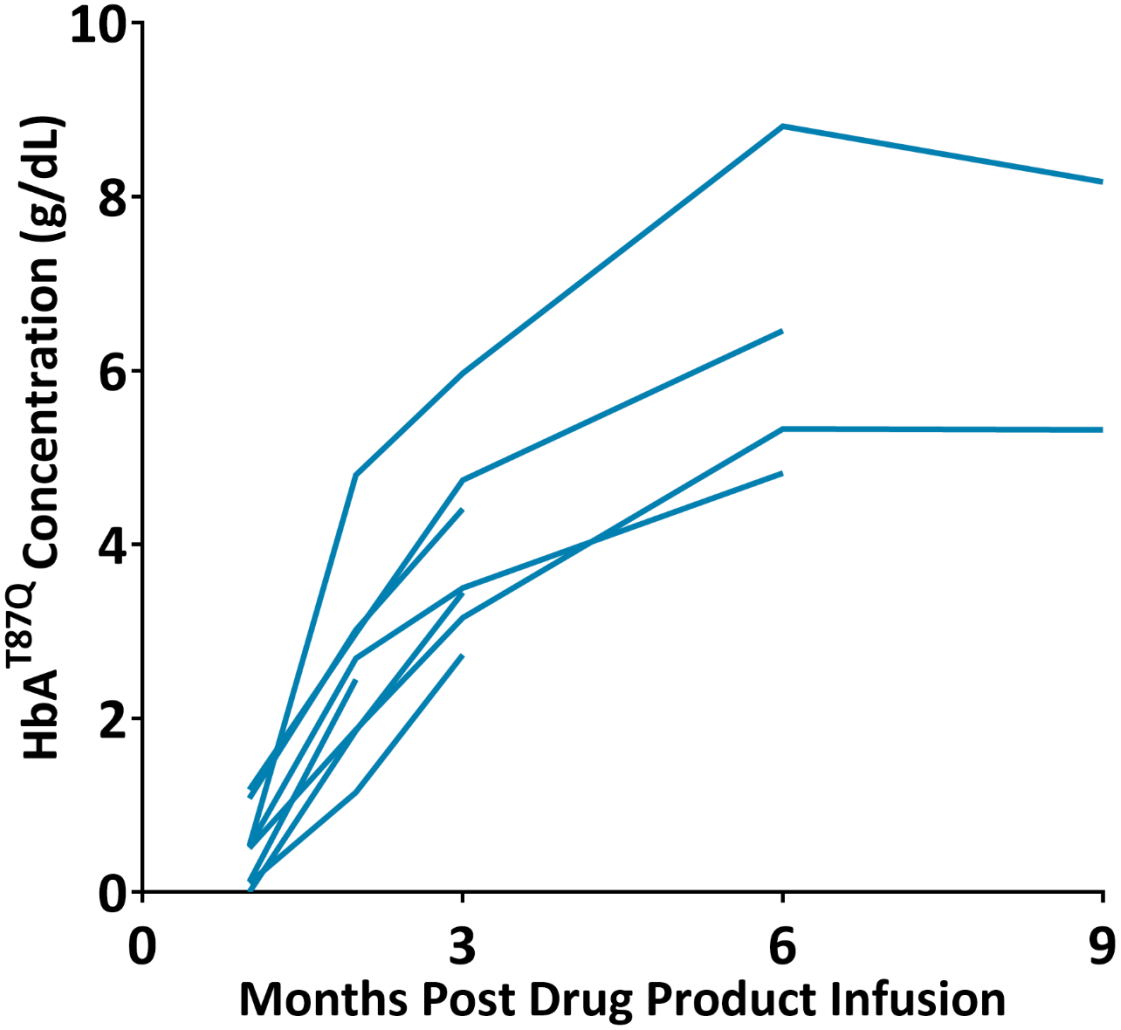
DP, drug product; VCN, vector copy number

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

Peripheral blood VCN

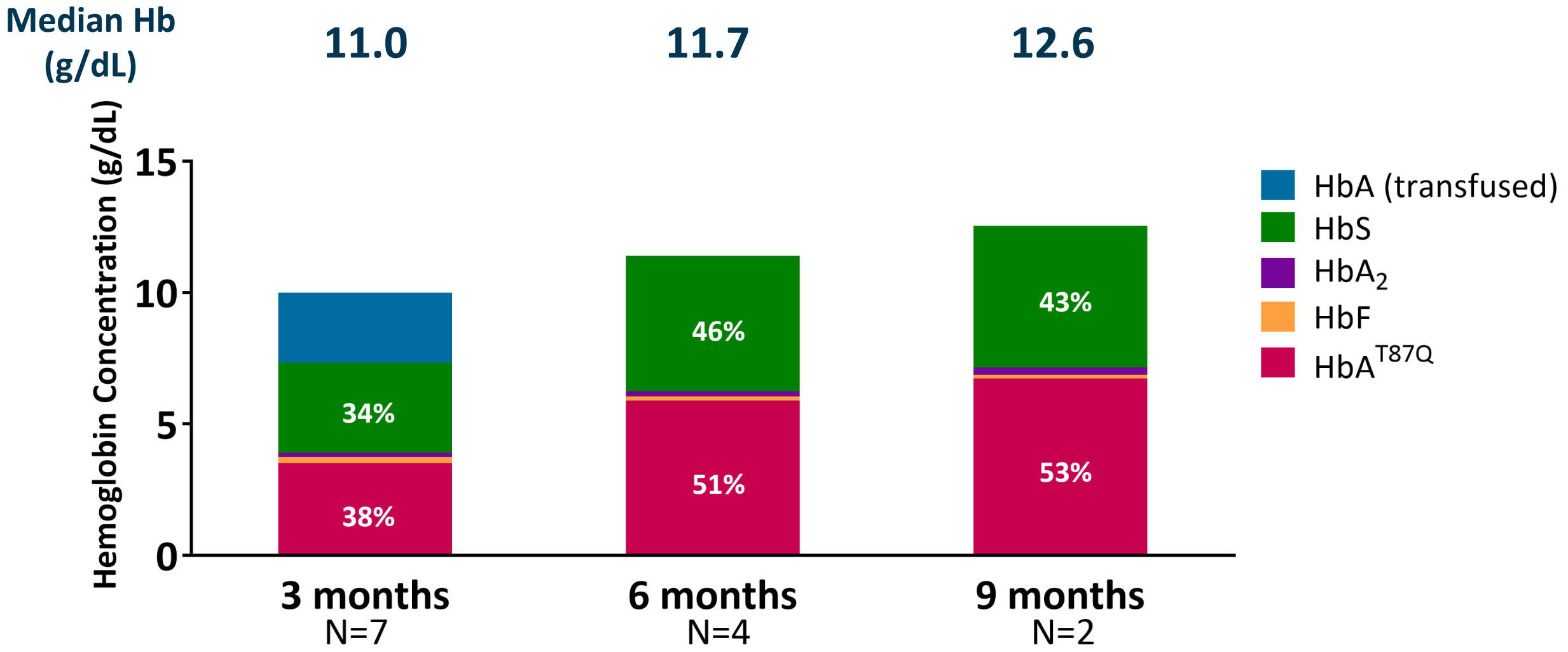


HbA^{T87Q} levels



Hb, hemoglobin; VCN, vector copy number

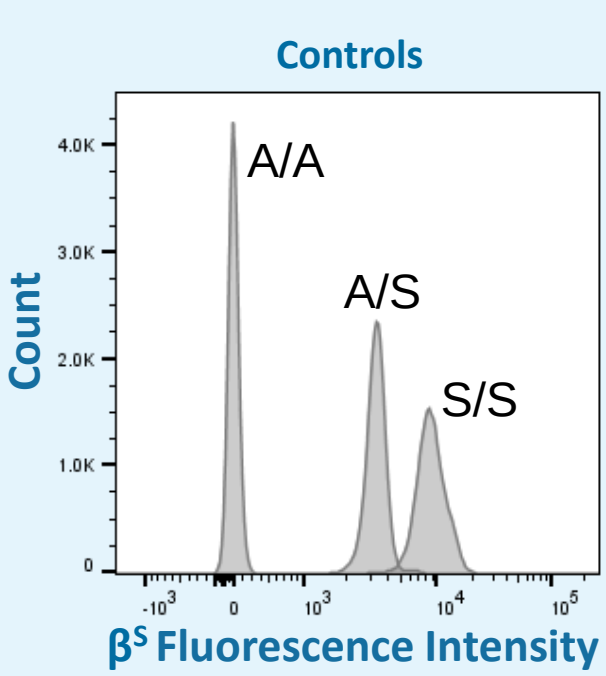
HGB-206 Group C: Gene therapy-derived Hb (HbA^{T87Q}) equals or exceeds HbS levels at ≥ 6 months

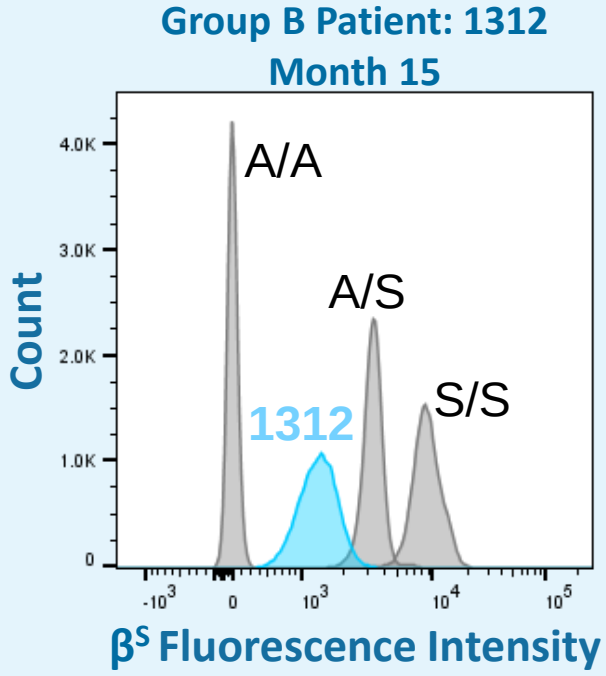


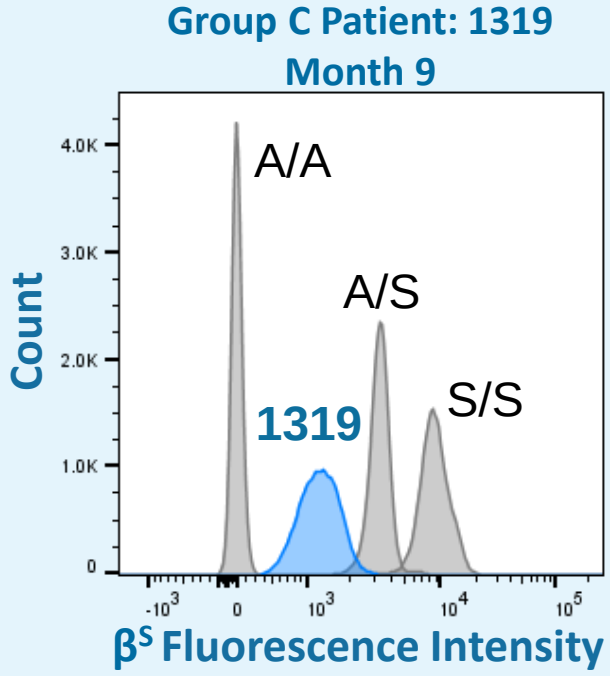
% represent median Hb fractions as % of total

Intracellular staining of RBCs with anti-β^S antibody suggests pancellular distribution of gene therapy-derived HbA^{T87Q} is achievable

- Exploratory assay: using an antibody that recognizes β^S, performed intracellular staining of RBCs followed by FACS analysis
  - Fluorescence intensity (X-axis) indicates amount of β^S in cells in sample
  - Control A/A, A/S, and S/S samples showed clearly distinct β^S intensity distributions, with S/S > A/S > A/A
- **Initial results in 2 patients 9 and 15 months post treatment show that nearly all RBCs have lower β^S intensity than S/S, and even A/S, samples**
  - Most non-β^S globin in these samples is $\beta^{A\text{-}T87Q}$ – patients are off transfusions and HbF < 2.5% of total globin chains





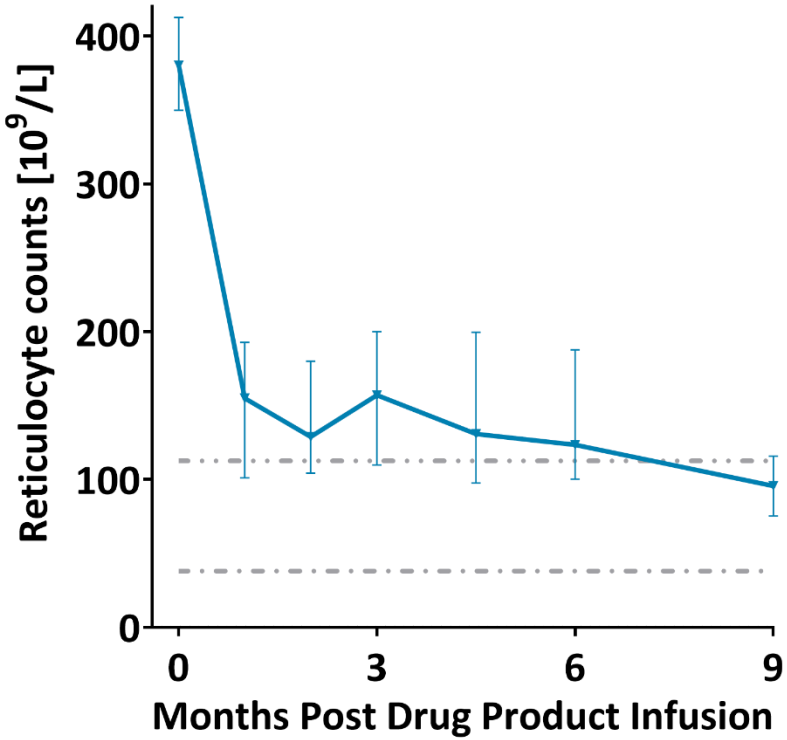


Blood Controls:
A/A = Healthy Donor
S/S = Sickle Cell Disease
A/S = Sickle Trait

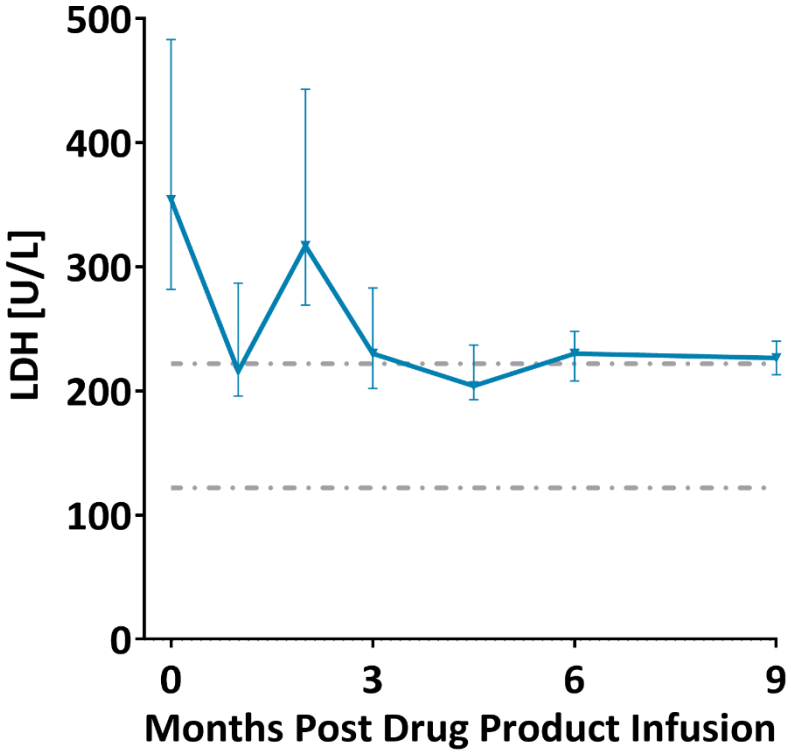
FACS, fluorescence-activated cell sorting; RBCs, red blood cells

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

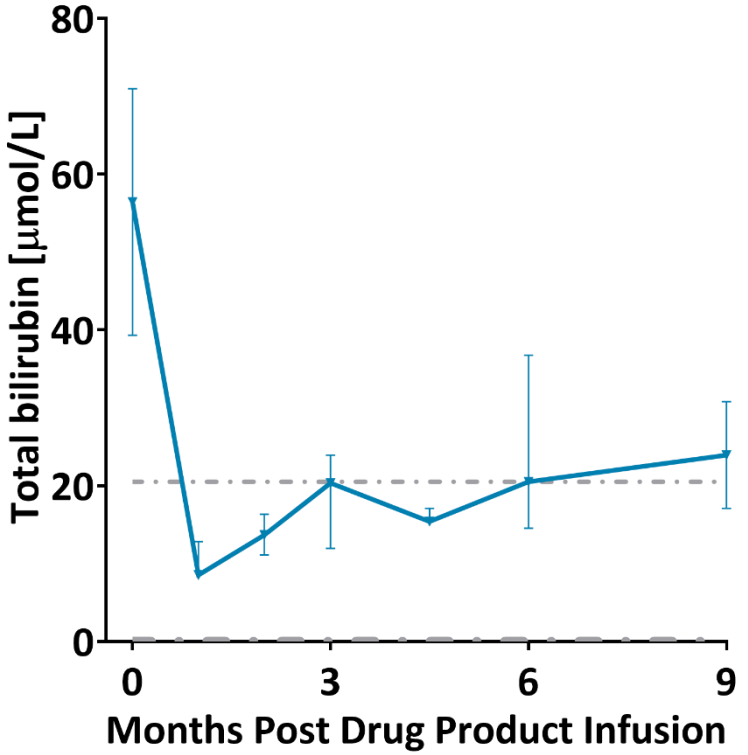
Reticulocyte Counts



Lactate Dehydrogenase

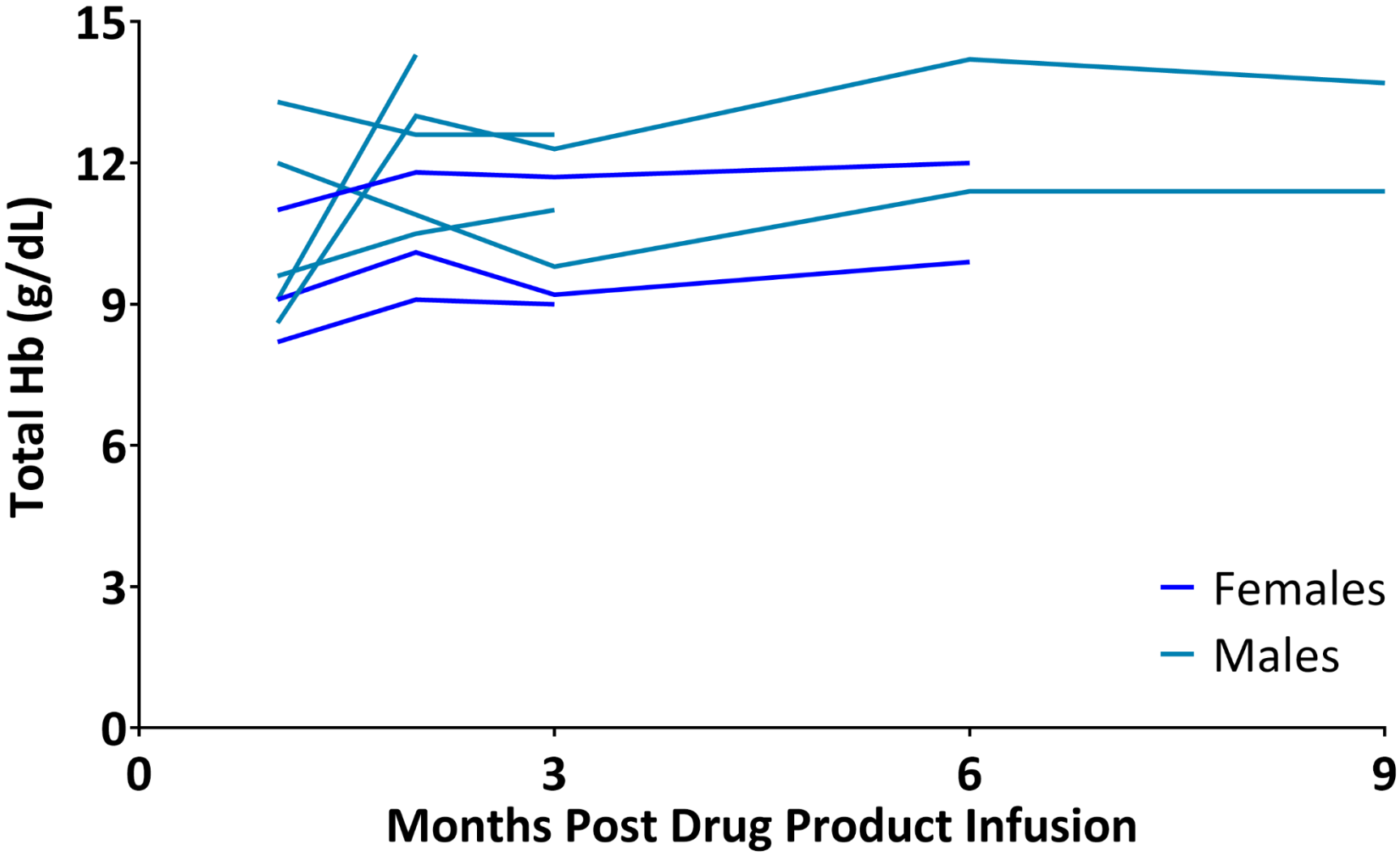


Total Bilirubin



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

HGB-206 Group C: Stable unsupported Hb levels over 3 – 9 months follow-up



Hb, hemoglobin

HGB-206 Group C: Summary

- LentiGlobin gene therapy in patients with severe SCD demonstrates an acceptable safety profile
- Refined manufacturing using plerixafor-mobilized HSCs generates robust HbA^{T87Q} production of 4.8 – 8.8 g/dL at ≥ 6 months that equals or exceeds HbS levels
  - Total unsupported Hb of 9.9 – 13.7 g/dL at last visit
  - Decreased hemolysis following LentiGlobin gene therapy
- No VOEs observed in any Group C patient following LentiGlobin treatment
- Data further support safety and feasibility of plerixafor mobilization and apheresis in SCD
- Exploratory translational assay suggests pancellular expression of gene therapy-derived Hb
- Protocol amended with expanded enrollment and modified endpoints to further evaluate the clinical impact of LentiGlobin gene therapy in SCD

Hb, hemoglobin; HSC, hematopoietic stem cell; VOE, vaso-occlusive event

Updates to HGB-206: An open-label, multicenter phase 1/2 study of LentiGlobin BB305 Drug Product 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 initiated August 2014

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

HGB-206 Study sites and investigators

Thank you to the study participants and their families

Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University

- Alexis Thompson
- Katherine Hammond

Medical University of South Carolina, Charleston

- Julie Kanter
- Michelle Hudspeth
- Brandi Day
- Jennifer Jaroscak

Children's Hospital of Philadelphia, UPenn

- Janet Kwiatkowski
- Pranaya Venkatapuram

UCSF Benioff Children's Hospital, Oakland

- Mark Walters
- Cyrus Bascon
- Marci Moriarty
- Frans Kuypers

Emory University, Atlanta

- Lakshmanan Krishnamurti
- Ashley Dulson
- Megan Hanby

National Institutes of Health, Molecular and Clinical Hematology Branch, Bethesda

- John Tisdale
- Matt Hsieh
- Wynona Coles
- Naoya Uchida
- Stephanie Helwing

Columbia University Medical Center

- Markus Mapara
- Monica Bhatia
- Julia Gould

bluebird bio, Inc.

- Erin Whitney
- Ying Chen
- Calvin Lee
- Iva Kronja
- Sarah Hunter
- Liz Macari
- Purvi Mody