ASGCT 2020 Abstract #1298

Resolution of Sickle Cell Disease (SCD) Manifestations in Patients Treated with LentiGlobin Gene Therapy: Updated Results from the Phase 1/2 HGB-206 Group C Study

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ASGCT 2020

- Disclosure of Affiliations: John F. Tisdale
- Nothing to Disclose

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 patients†

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

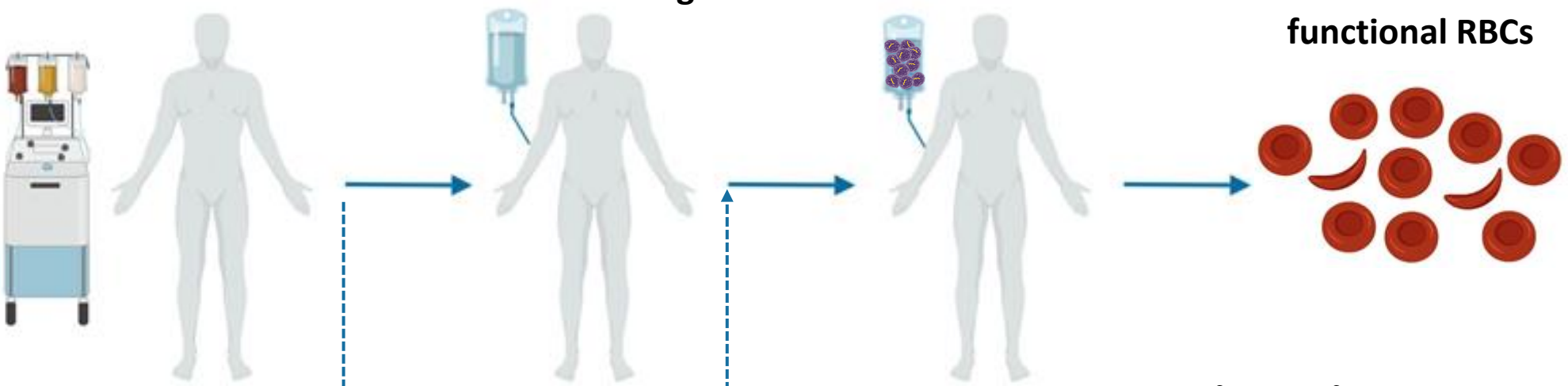
LentiGlobin for SCD Gene Therapy Overview

HSC collection
Mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

DP infusion

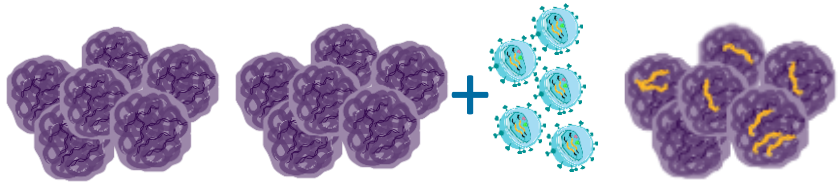
Transduced HSCs engraft and contribute to reconstitution of functional RBCs



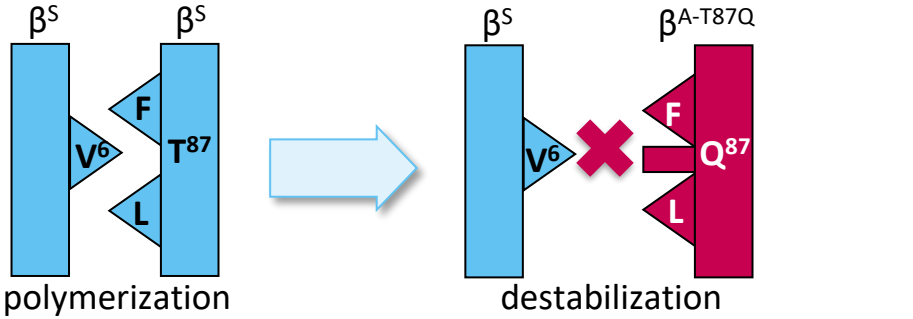
2-yr follow-up

Long-Term Follow-Up Study

LentiGlobin DP centralized manufacturing



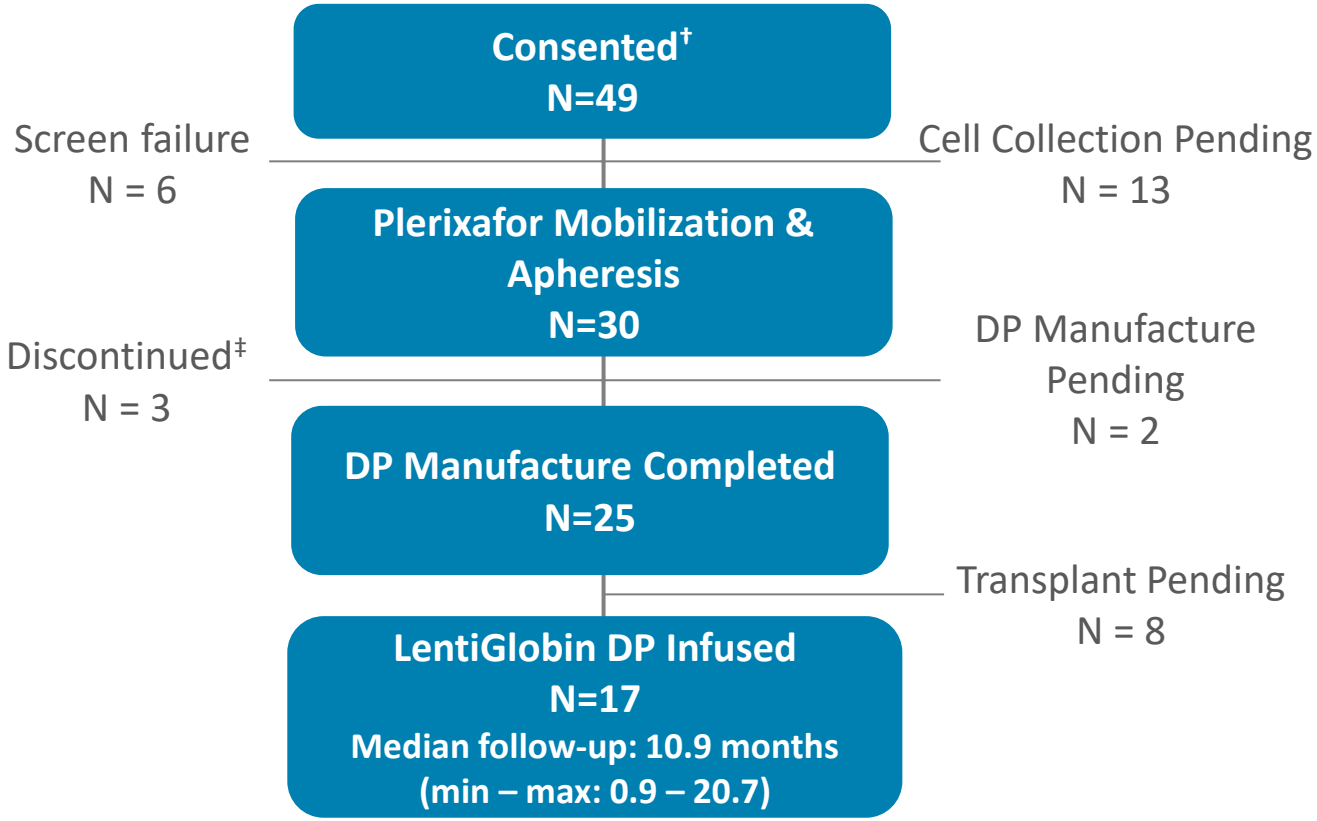
Select CD34+ cells ***Transduce with BB305 lentiviral vector*** ***Cryopreserve, test, release DP***



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

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

HGB-206 Group C: 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

N=30 Patients who Started Cell Collection

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**

[*]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

N=17 Infused Patients

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)

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** 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** n (%)
Nausea	2 (11.8)
Vomiting	2 (11.8)

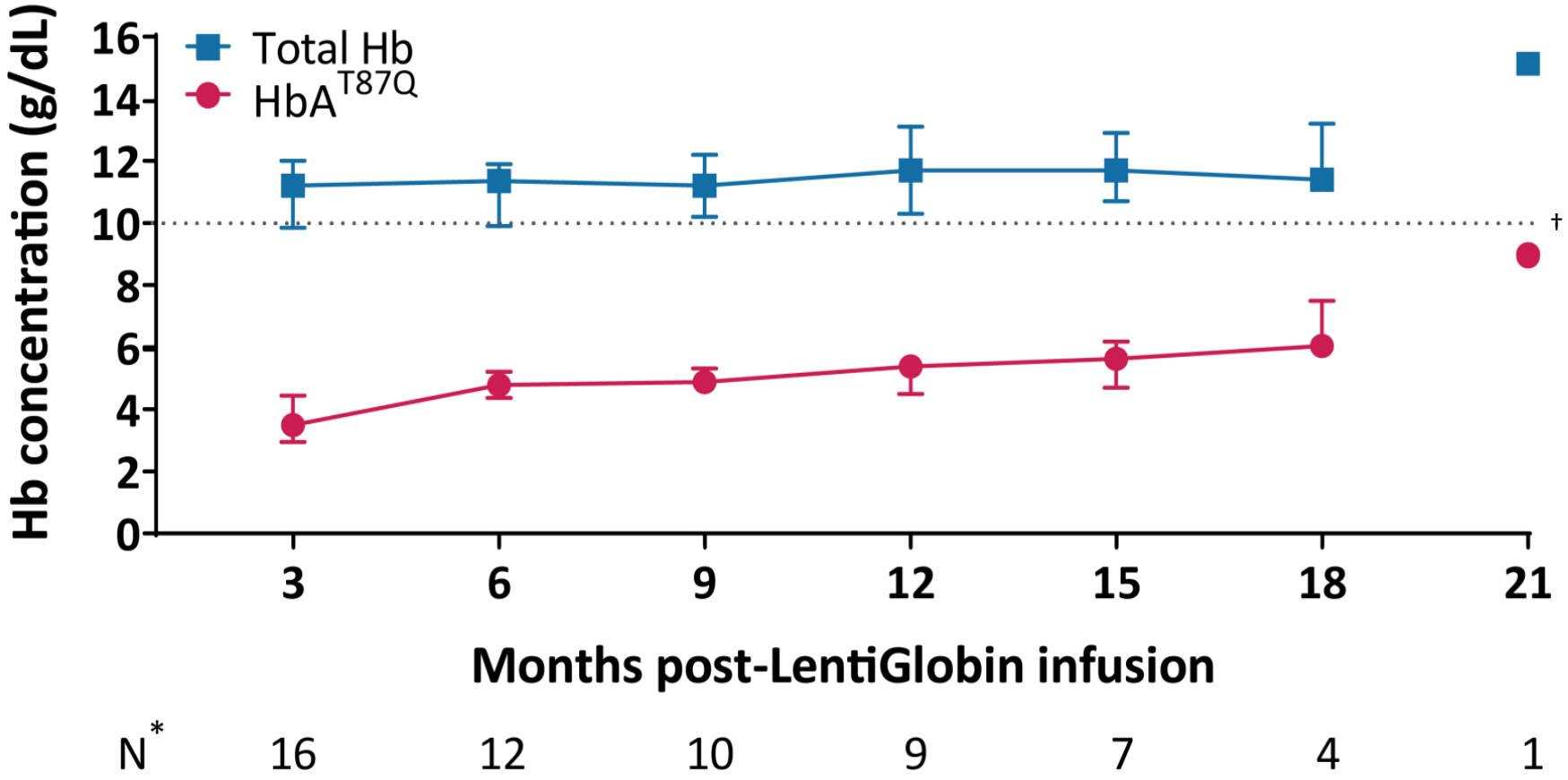
*Hematologic AEs commonly observed post-transplantation have been excluded

RCL, replication competent lentivirus

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

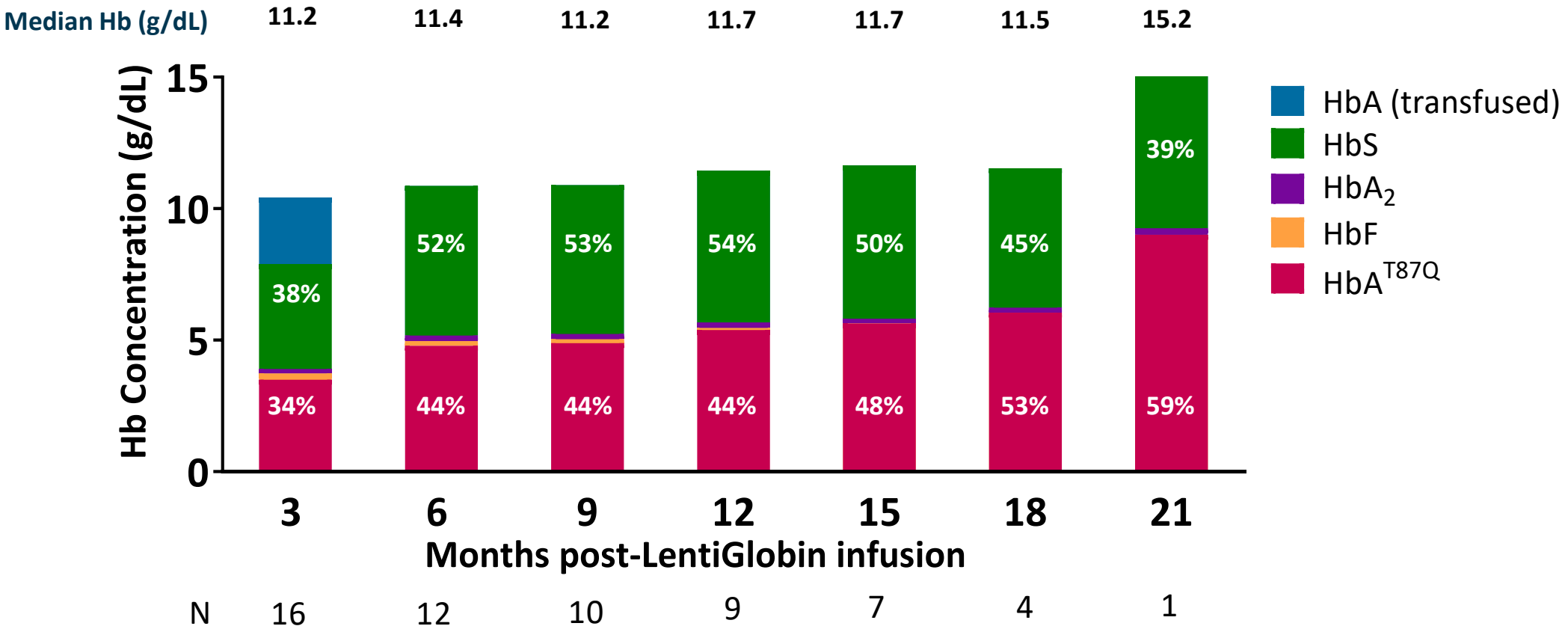
HGB-206 Group C: HbA^{T87Q} and Total Hb Over Time



- Median total Hb at screening was 9.3 (6.8 – 12.2) g/dL (includes some patients on chronic transfusions)
- Median total Hb is maintained at 10 g/dL post-LentiGlobin treatment with stable levels of HbA^{T87Q}

*Shows number of patients for whom data are available, Median (Q1, Q3) depicted; †Key outcome includes total Hb ≥ 10 g/dL

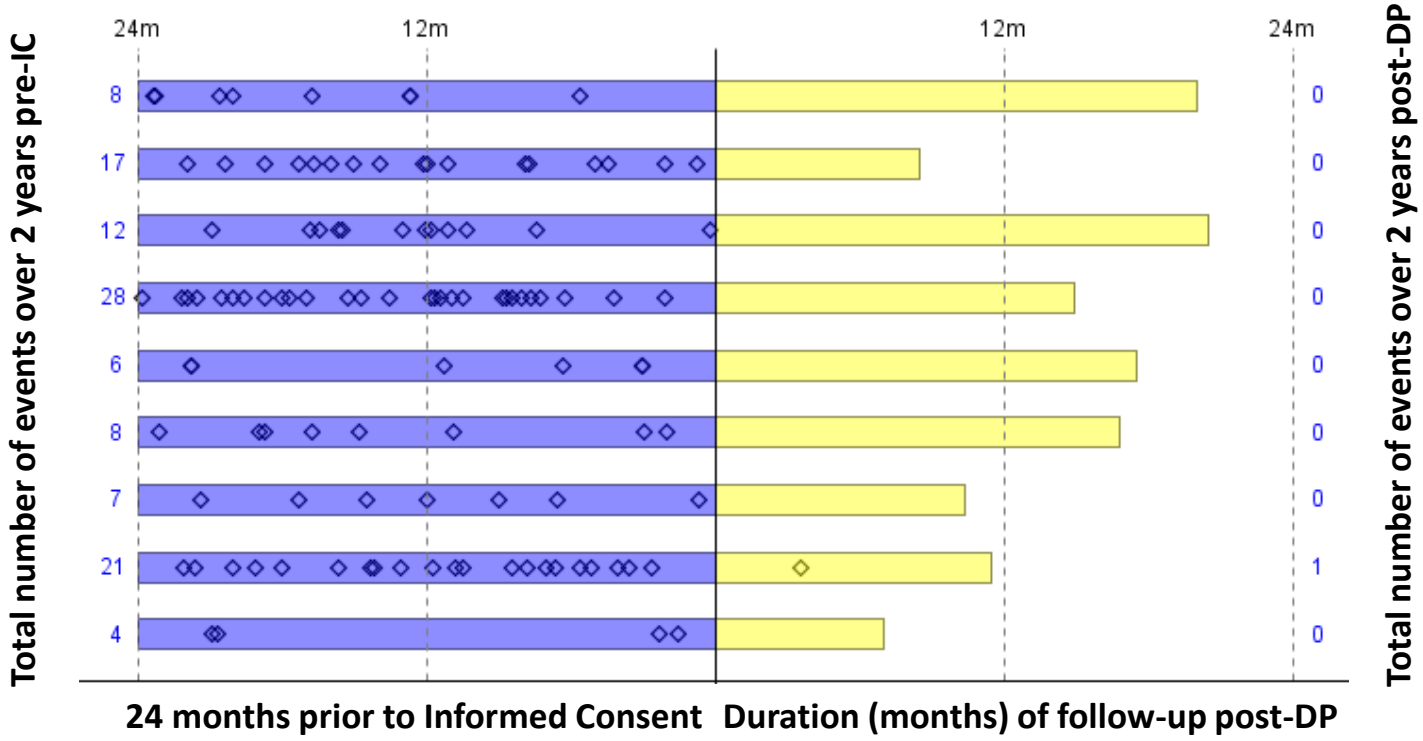
HGB-206 Group C: Hemoglobin Fractions Post-LentiGlobin Treatment



- 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: Reduction of VOC + ACS Post-LentiGlobin Treatment



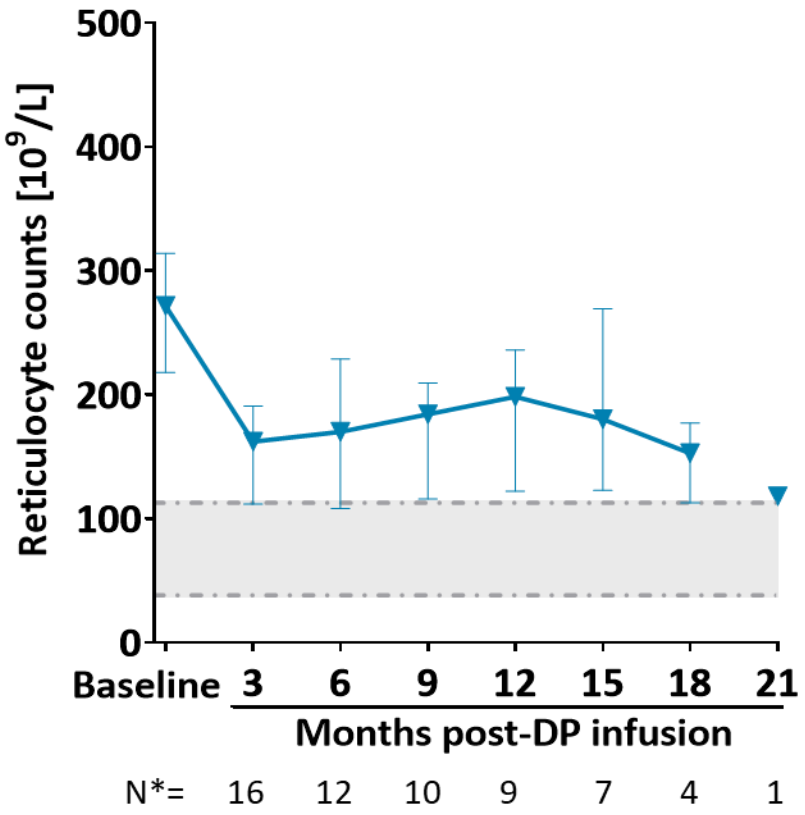
- The reduction of annualized rate is 99% [95% confidence interval, 92.5 – 100%]
- No ACS or serious VOCs occurred in any Group C patient post-LentiGlobin treatment to date (between 1-21 months follow-up)
- As previously reported, 1 non-serious Grade 2 VOC was observed in 1 patient ~ 3.5 months post-LentiGlobin 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

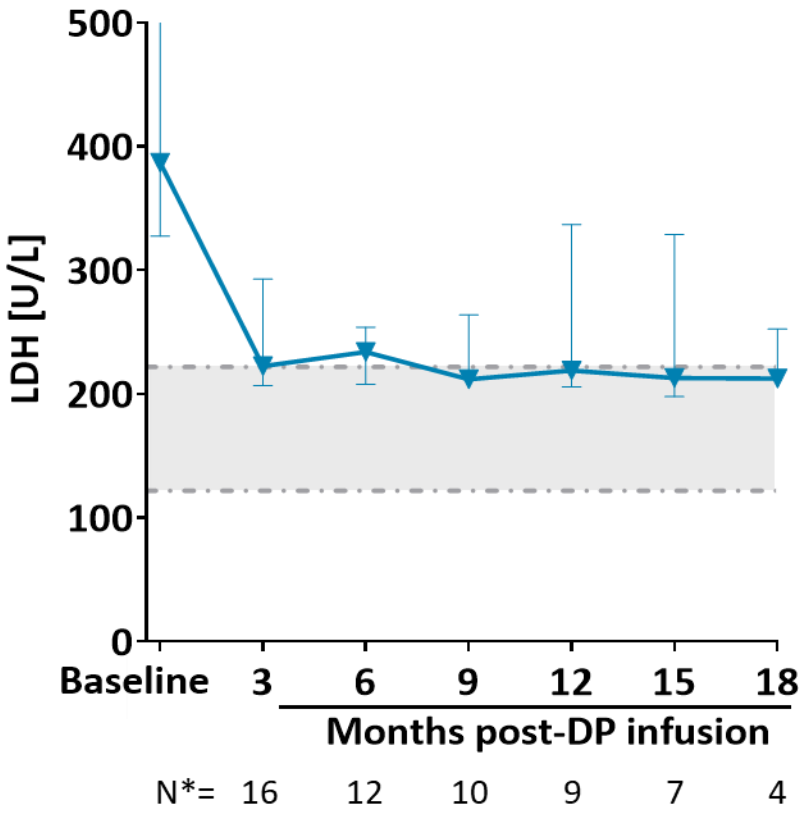
DP, drug product; IC, informed consent

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

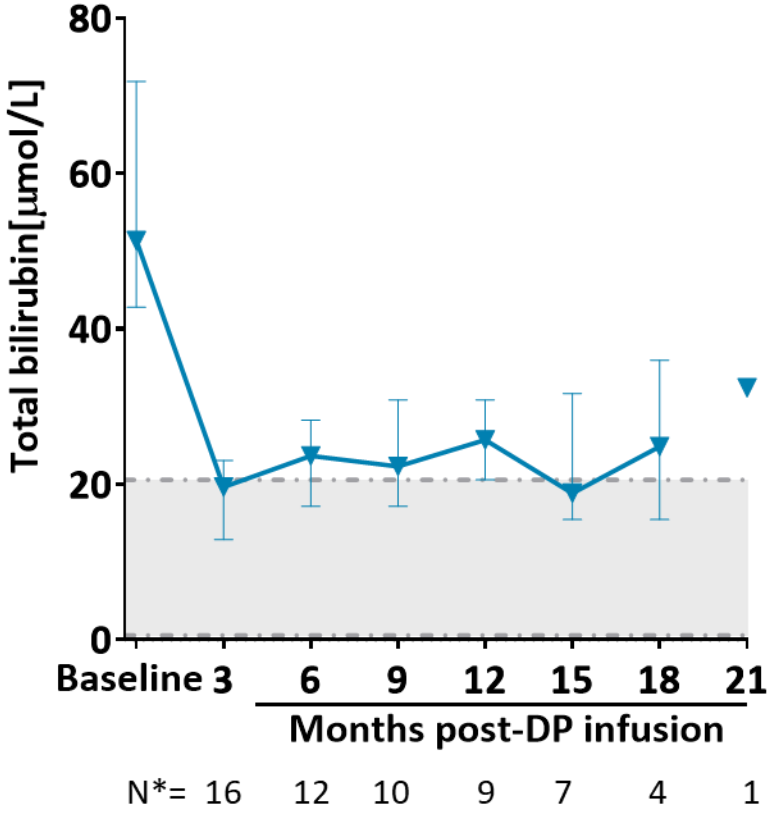
Reticulocyte Counts



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

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 serious VOCs or ACS were observed post-DP treatment in Group C patients with 1 to 21 months follow-up
  - The annualized VOC+ACS rate was reduced by 99% [95% confidence interval, 92.5 – 100%], from median of 4.0 pre- to 0 post-DP treatment
- 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
- 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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