# LentiGlobin Gene Therapy in Patients with Sickle Cell Disease: Updated Interim Results from HGB-206

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# HGB-206: Study of LentiGlobin gene therapy for severe sickle cell disease (SCD)

## 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, Hb, Hb fractions
  - Vector copy number in peripheral blood

**Study initiated August 2014**

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

Data as of September 14, 2018

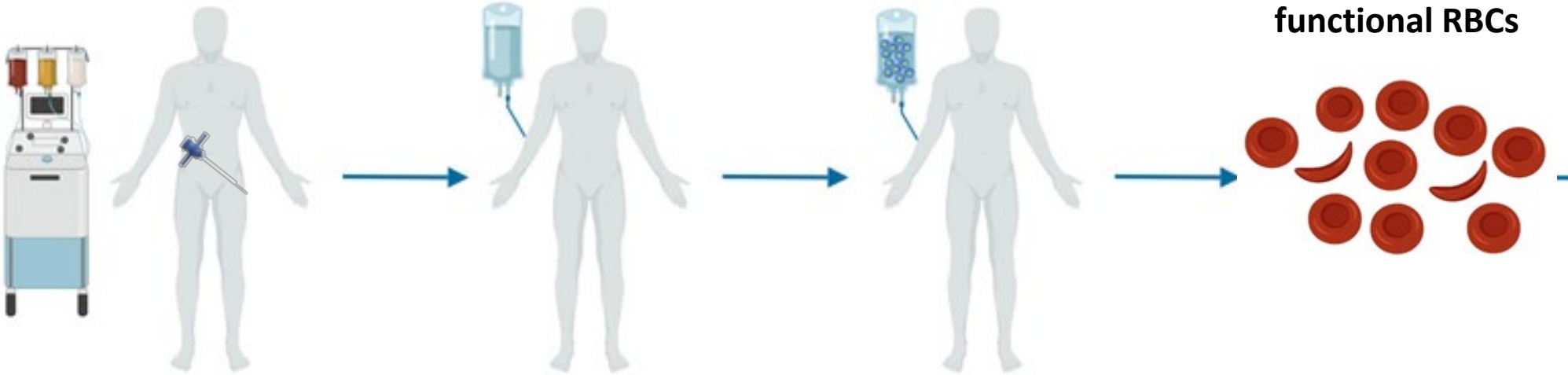
# LentiGlobin gene therapy overview in patients with SCD

**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**



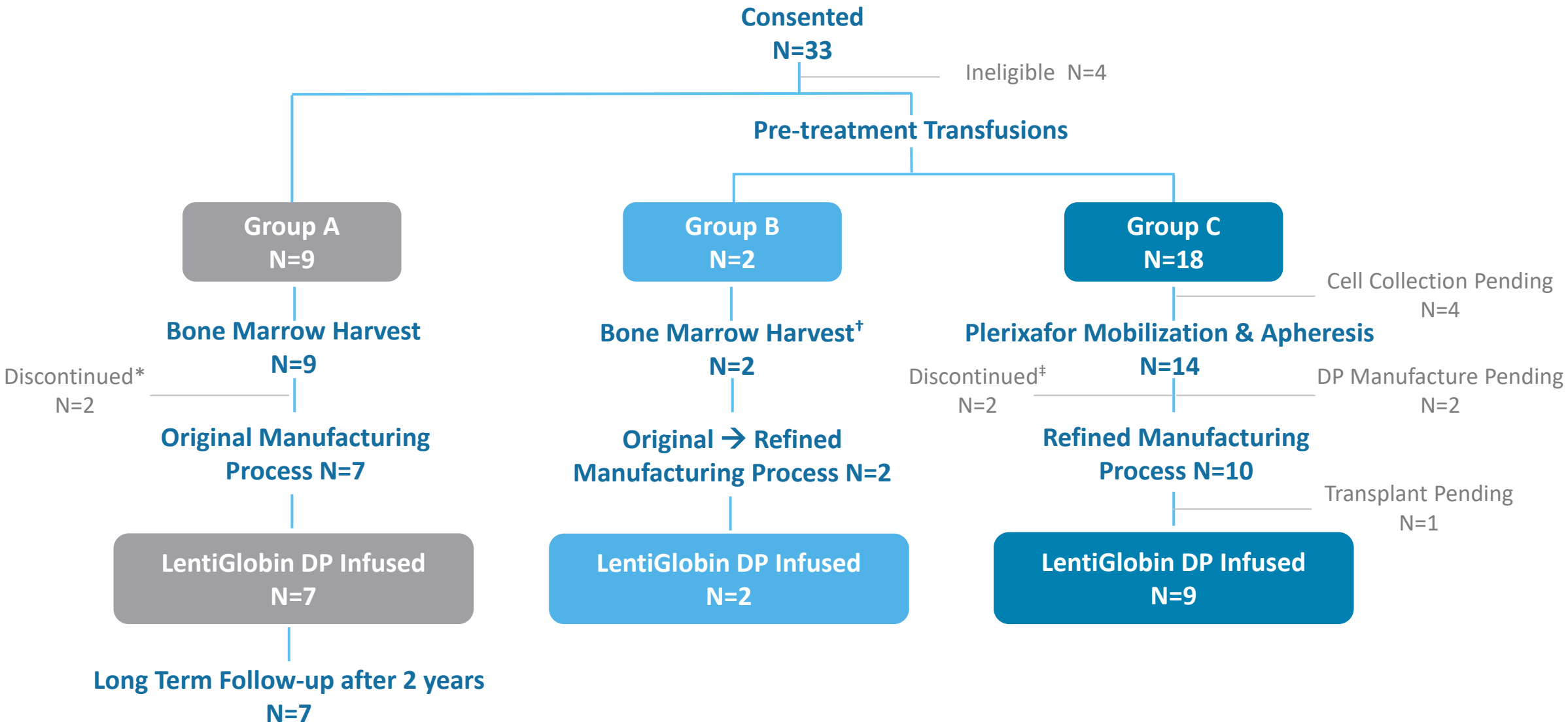
**2-yr follow-up**

**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

# Study disposition




*1 due to insufficient cell collection, 1 withdrew consent; †1 patient also received a single mobilization cycle to collect cells for back-up; ‡1 due to adverse event, 1 withdrew consent

Data as of September 14, 2018

# Patient characteristics

*N=25 patients who started cell collection*

| Parameter | Group A N=9 | Group B N=2 | Group C N=14 |
|---|---|---|---|
| **Age at consent**, years<br>median (min – max) | **26**<br>(18 – 43) | **24.5**<br>(22 – 27) | **25.5**<br>(18 – 36) |
| **Gender** | **2 F 7 M** | **0 F 2 M** | **6 F 8 M** |
| **Genotype,** $\beta^S/\beta^S$ | **9** | **2** | **14** |
| **SCD History** | | | |
| **Hydroxyurea**, n | **5** | **2** | **8** |
| **VOCs***, n<br>Annualized no. of events, median (min – max) | **7**<br>**4.5** (2.0 – 27.5) | **2**<br>**10.0** (2.5 – 17.5) | **9**<br>**6.5** (3.5 – 14.0) |
| **ACS**†, n<br>Annualized no. of events, median (min – max) | **1**<br>**1** | **1**<br>**1** | **2**<br>**1** (1 – 1) |
| **Stroke**, n | **2** | **0** | **3** |
| **TRJV >2.5 m/s**, n | **1** | **0** | **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

# Treatment characteristics

*N=18 infused patients*

| Parameter | Group A N=7 Median (min – max) | Group B N=2 (Pt 1312, Pt 1313) | Group C N=9 Median (min – max) |
|---|---|---|---|
| **No. of bone marrow harvests** | **2** (1 – 4) | **2, 3** | N/A |
| **No. of mobilization cycles** | N/A | 1[‡] | **2** (1 – 3) |
| **No. of apheresis procedures per mobilization cycle** | N/A | 1 | **1** (1 – 2) |
| **CD34+ cells collected per collection cycle,** x$10^6$ cells/kg | **4.0** (0.1 – 10.8) | **6.3**[#], **1.2**[#] | **9.2** (5.6 – 21.6) |
| **Average busulfan AUC,** µM*min (over 4 days) | **4747** (4084 – 5290)[§] | **5256, 5017** | **4787** (4608 – 5182) |
| **Follow-up,** months | **29.9** (29.2 – 38.9) | **14.3, 17.2** | **5.2** (0.5 – 9.2) |
| **Neutrophil engraftment,** days (ANC ≥ 500 /µl) | **22** (17 – 29) | **23, 28** | **19.5** (18 – 24)[^] |
| **Platelet engraftment,** days (platelets > 50k /µl) | **56** (29 – 63) | **31, 61** | **28** (19 – 136)[¶] |

[‡]For research purposes; [#]Median per BMH; [§]Based on data for 6 patients; [^]Based on data for 8 patients; [¶]Based on data for 7 patients

- 6/7 Group C patients had platelet engraftment by Day 90

# Safety profile with plerixafor mobilization/apheresis vs bone marrow harvest (BMH)

**In 26 BMHs in 11 patients, 18 Grade ≥ 3 AEs were reported in 6 patients***

| Patients with Grade ≥ 3 AEs within 7 days of BMH | n (%) N=11 |
|---|---|
| Procedural pain[1] | 6 (54) |
| Anemia | 2 (18) |
| Vaso-occlusive pain[2] | 2 (18) |
| Lymphocyte count increased | 1 (9) |

[1]Considered serious in 2 patients; [2]3 events in 2 patients, all considered serious

**In 35 apheresis procedures in 14 Group C patients†, 5 Grade ≥ 3 AEs were reported in 3 patients**

| Patients with Grade ≥ 3 AEs within 7 days of 1st plerixafor in a mobilization cycle | n (%) N=14 |
|---|---|
| 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

*Patient could have experienced same AE more than once; †Plerixafor mobilization/apheresis for research purposes was performed in 1 Group B patient, resulting in 3 Grade 3 AEs: vaso-occlusive pain, increased AST and increased ALT

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; VOE, vaso-occlusive event

# Safety profile consistent with myeloablative busulfan conditioning

| **Non-hematologic Grade ≥ 3 AEs*** *Post DP infusion in ≥ 2 patients* | **n (%) N=18** |
|---|---|
| Stomatitis | 13 (72) |
| Febrile neutropenia | 11 (61) |
| Vaso-occlusive pain | 5 (28) |
| Pharyngeal inflammation | 4 (22) |
| Bacteremia | 2 (11) |
| Dyspnea | 2 (11) |
| Epistaxis | 2 (11) |
| Non-cardiac chest pain | 2 (11) |
| Pyrexia | 2 (11) |

*Hematologic AEs commonly observed post-transplant have been excluded

- No cases of VOD
- No VOEs post DP infusion in Group C patients
- No graft failure, deaths or vector-mediated RCL
- No evidence of clonal dominance observed to date
- Serious AEs were reported in 12 patients, vaso-occlusive pain was most common (n=5; 4 in Group A & 1 in Group B)
  - **1 Grade 4 SAE of myelodysplastic syndrome (MDS) in Group A patient**

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

Data as of September 14, 2018

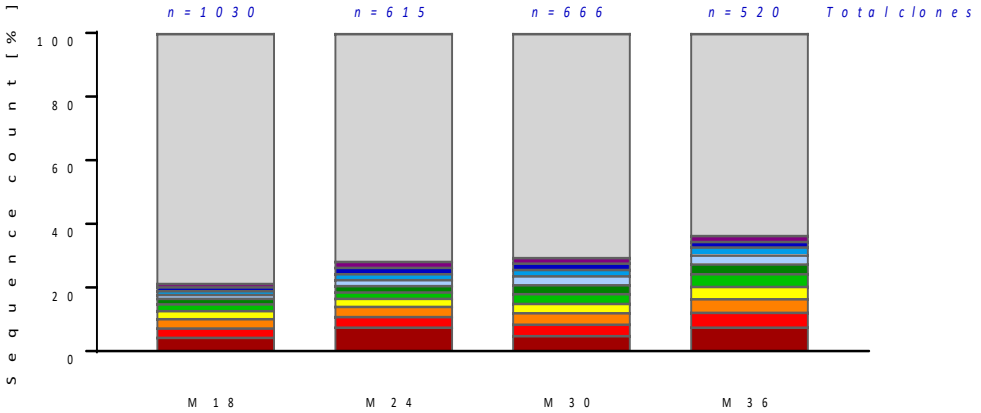
# A case of myelodysplastic syndrome with excess blasts in a patient >40 years old

- **Grade 4 SAE of MDS in a Group A patient ~36 months post LentiGlobin infusion**
- **BM biopsy showed 15% myeloblasts/dysplasia with monosomy 7 and 19p abnormality in 8/20 metaphases**

**No evidence of clonal dominance** (No IS > 30%)

- Largest 5 clones varied over 18 months

**Frequencies of top 10 integration sites**




**Blast cells (CD34+) had low VCN consistent with no LVV genotoxicity**

| Marrow cell populations after MDS diagnosis | Purity (%) | VCN (c/dg) |
|---|---|---|
| Unsorted | N/A | 0.14 |
| CD34- | 98 | 0.21 |
| CD34+ blasts | 93 | 0.02 |

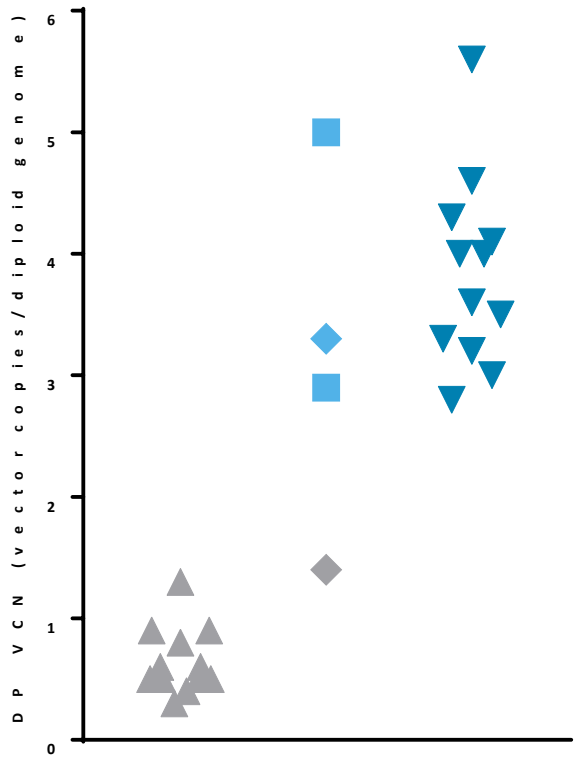
- Given LVV genotoxicity would cause VCN > 1 in CD34+ blasts, MDS SAE is considered unlikely related to LentiGlobin GT*
- MDS is a risk of autologous HSCT with alkylating agents such as busulfan[1-3]

*Per safety database; BM, bone marrow; c/dg, copies/diploid genome; GT, gene therapy; HSCT, hematopoietic stem cell transplant; IS, integration site; LVV, lentiviral vector; MDS, myelodysplastic syndrome; N/A, not applicable; VCN, vector copy number

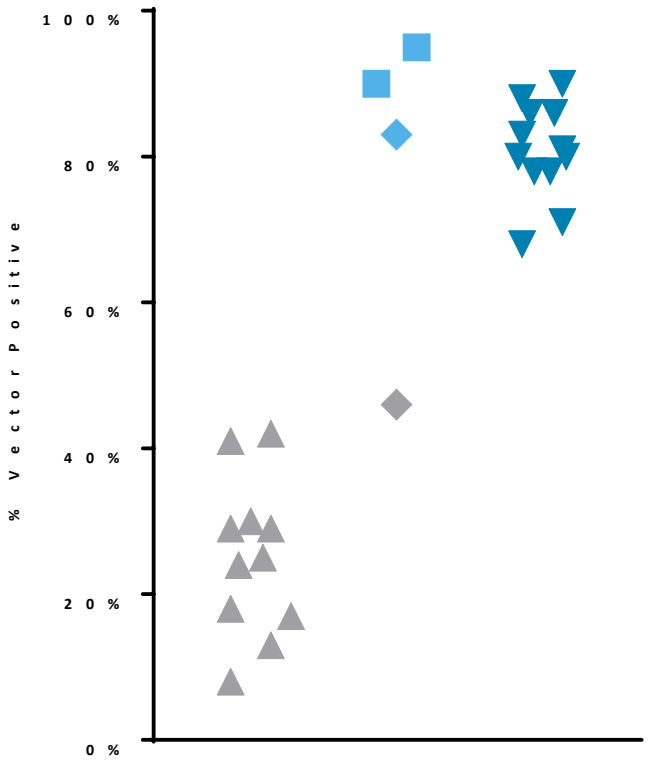
1. Rege KP et al., BMT 1998; 2. Howe R et al., BMT 2003; 3. McNerney ME et al., Nat Rev Cancer 2017

# Refinements to manufacturing and cell harvest improved drug product characteristics

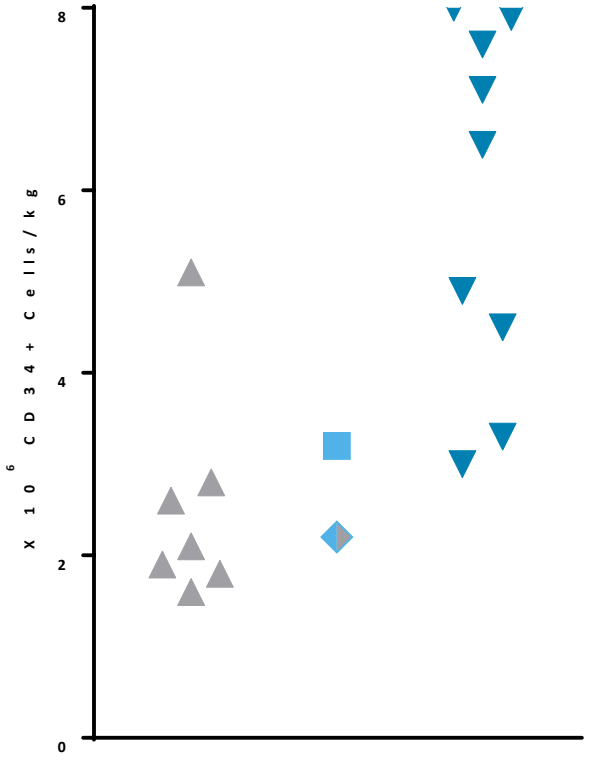
## Vector copy number




## % Transduced cells




## CD34+ cell dose




**LentiGlobin manufacturing process** (HSC source)

- **Original** (BM)
- **Refined** (BM)
- **Refined** (PB)

| Group | A | B | C |
|---|---|---|---|
| | N = 7 | N = 2 | N = 9 |
| | 12 DP† | 4 DP† | 12 DP† |
| **Median** | 0.6 | 3.1‡ | 3.8 |

| Group | A | B | C |
|---|---|---|---|
| | N = 7 | N = 2 | N = 9 |
| | 11 DP†# | 4 DP† | 12 DP† |
| **Median** | 25 | 87‡ | 81 |

| Group | A | B | C |
|---|---|---|---|
| | N = 7 | N = 2 | N = 9 |
| **Median** | 2.1 | 2.7 | 6.5 |

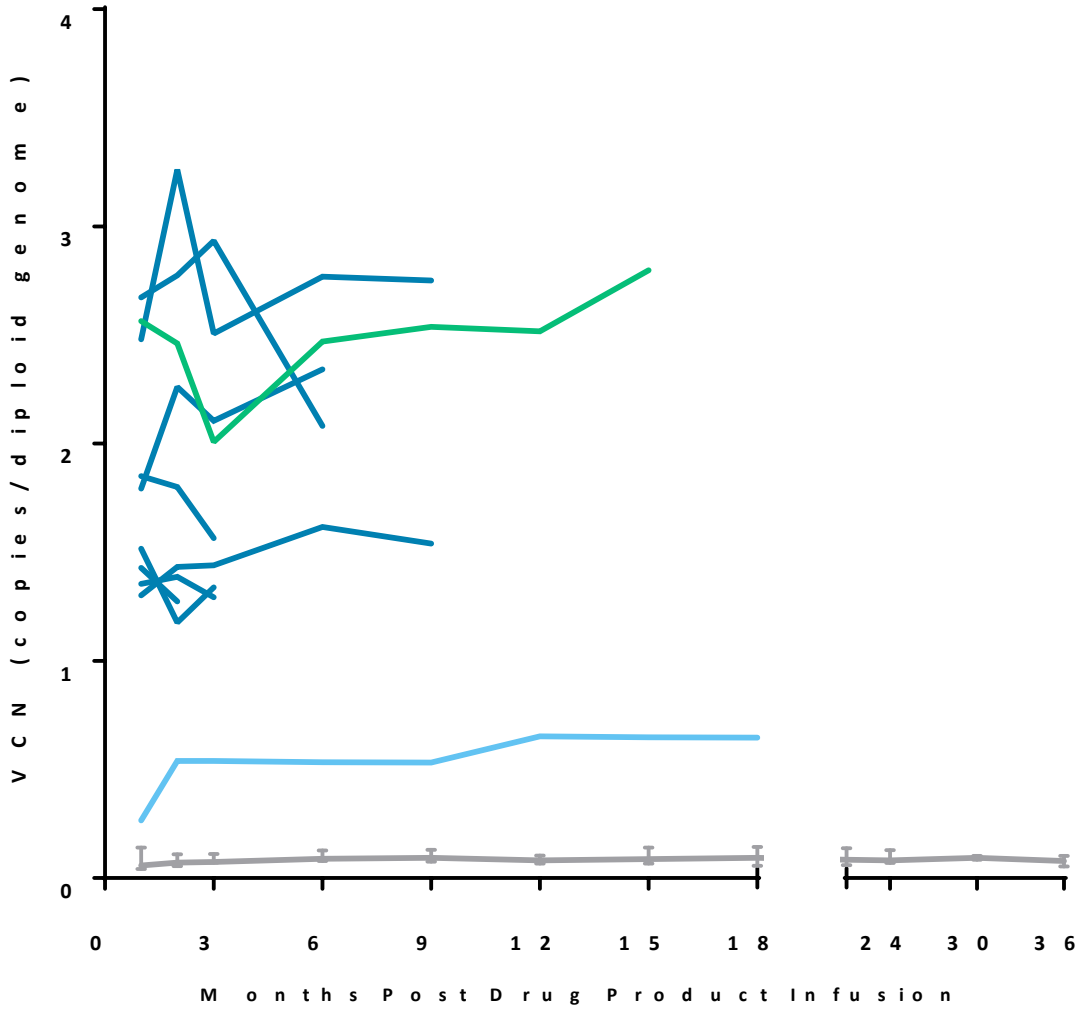
†Number of DP exceeds number of patients since some patients were harvested or mobilized more than once; # % Transduced cells not available for 1 DP at time of analyses; ‡1 Group B DP lot was made using original manufacturing process, while the other 3 DP lots were made using refined manufacturing process

BM, bone marrow; DP, drug product; HSC, hematopoietic stem cell; PB, peripheral blood; VCN, vector copy number

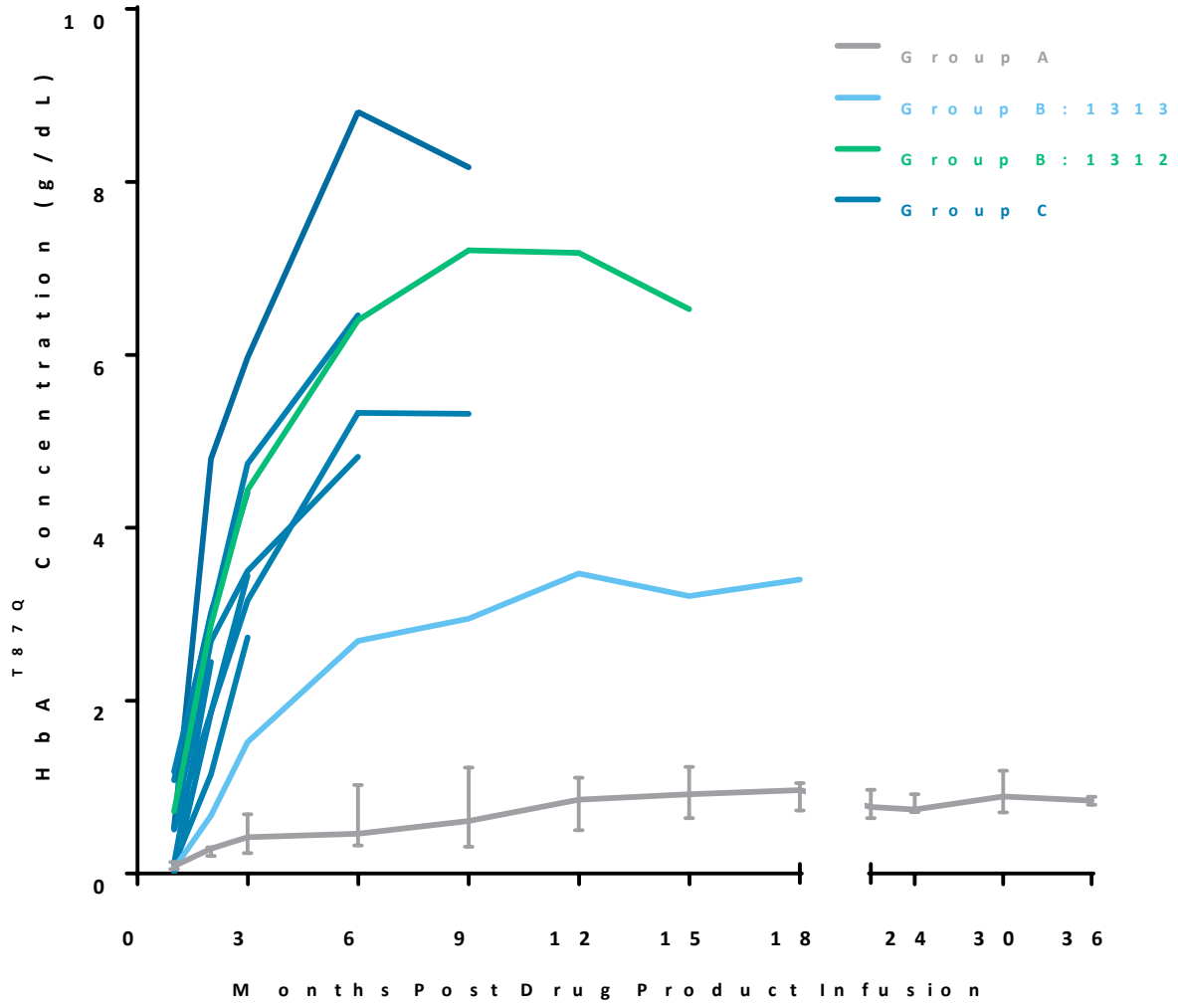
Data as of September 14, 2018

# Peripheral blood VCN and $HbA^{T87Q}$ over time

## Peripheral blood VCN



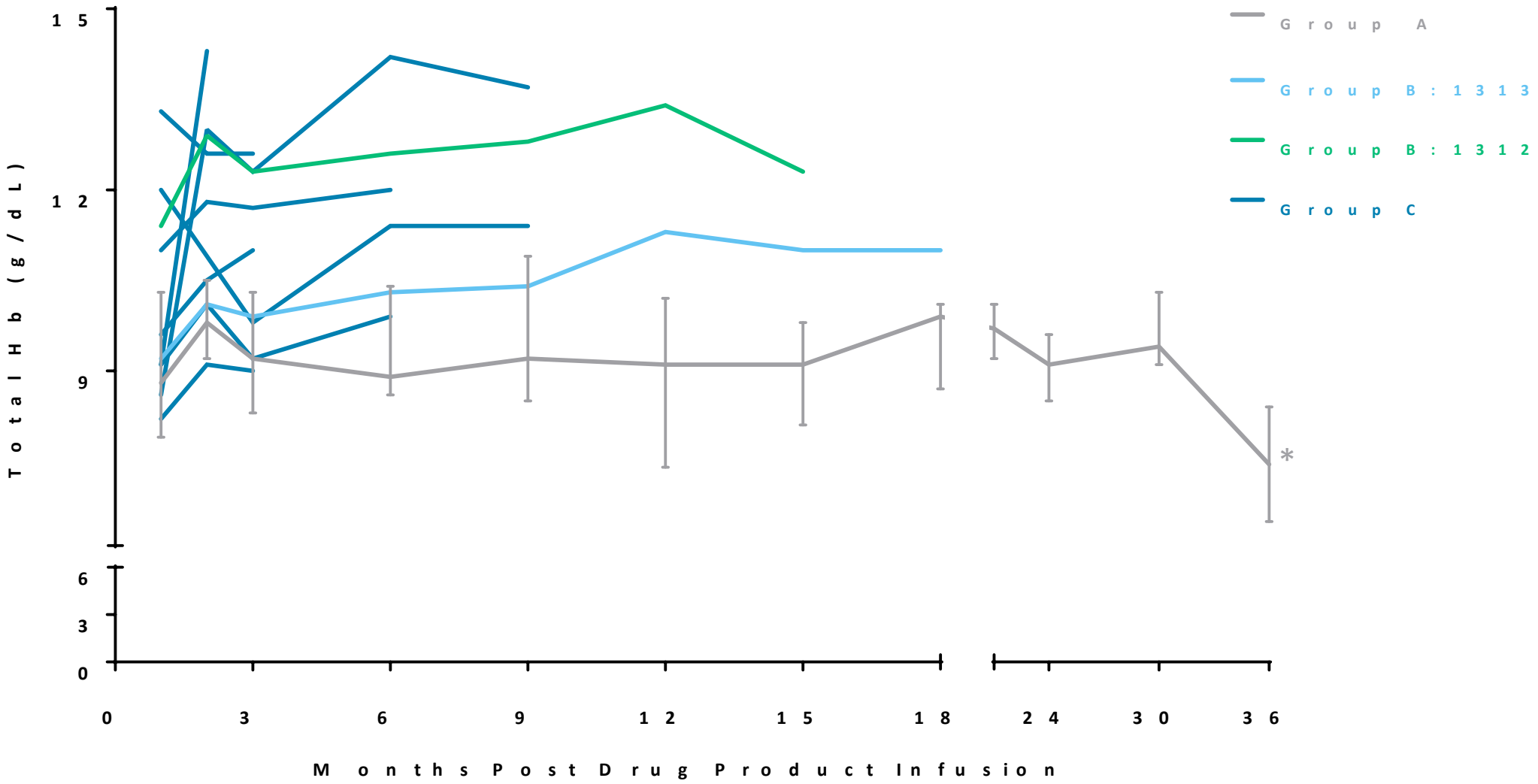

## $HbA^{T87Q}$ levels




For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 36 study visit (N=2); Hb, hemoglobin; VCN, vector copy number

Data as of September 14, 2018

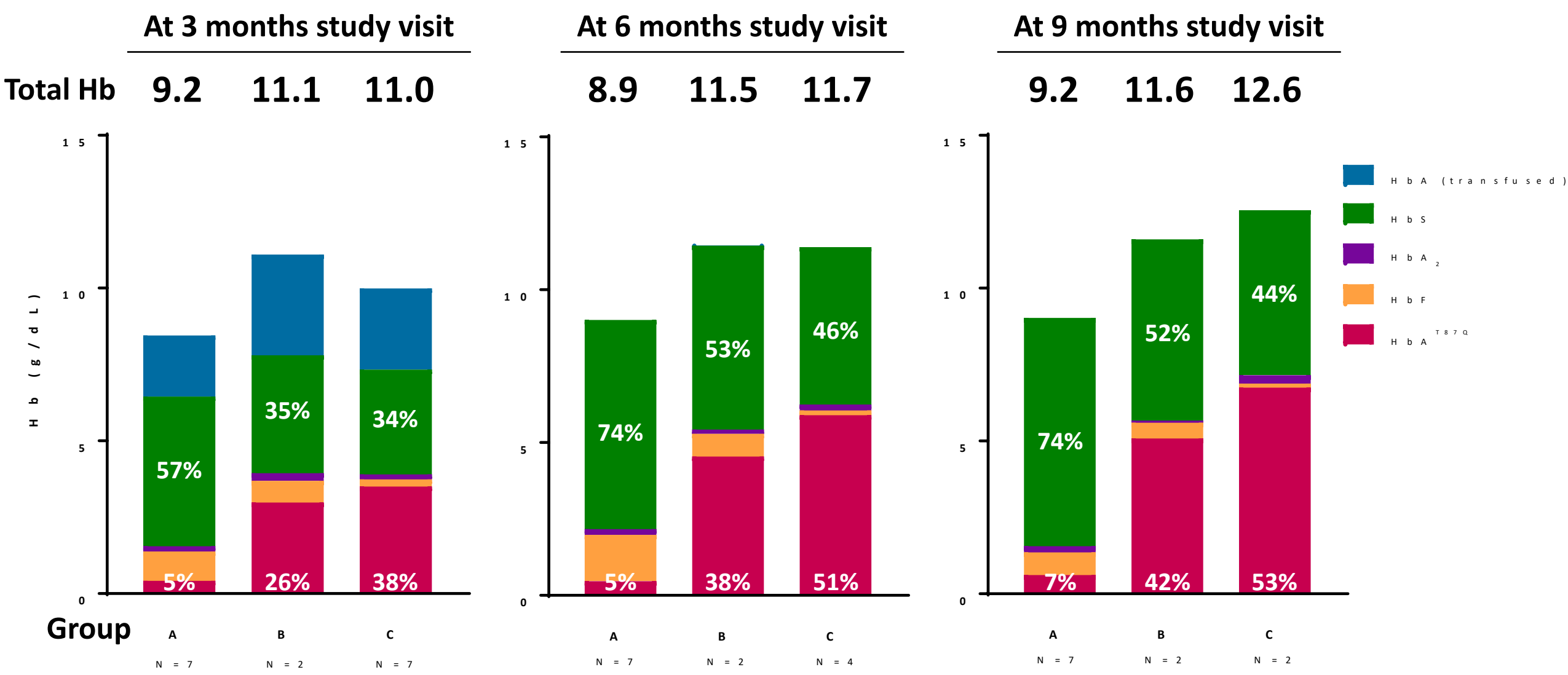
# Total Hb levels over time




*N=2 at 36 months

For Group A patients, medians (Q1, Q3) depicted; Hb, hemoglobin

# Gene therapy-derived Hb ($HbA^{T87Q}$) equals or exceeds HbS levels at ≥ 3 months in Group C patients

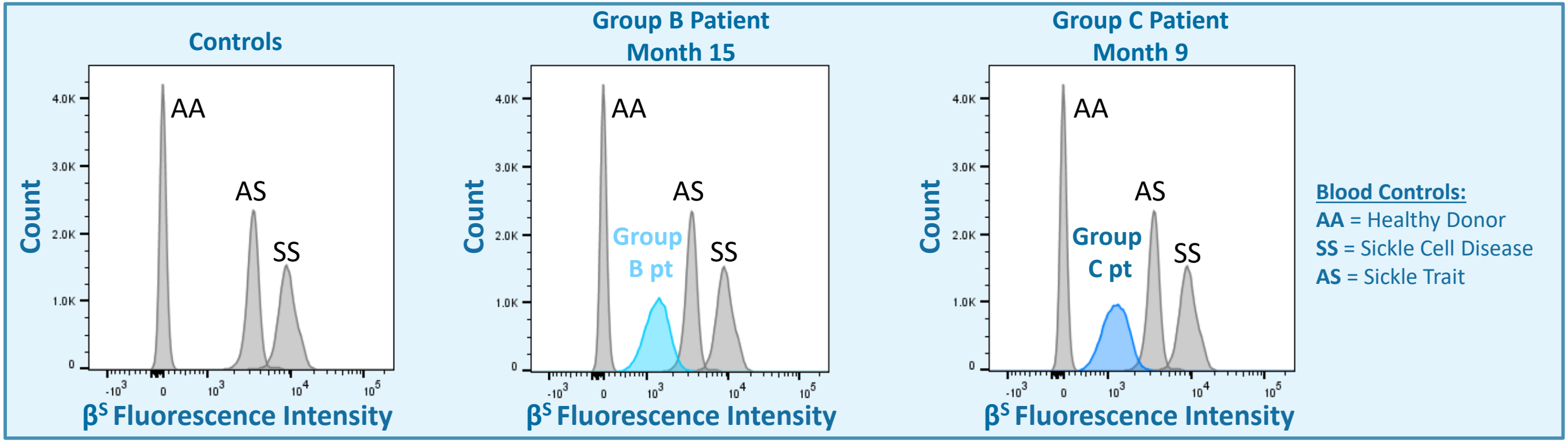



% represent median Hb fractions as % of total; Hb, hemoglobin

Data as of September 14, 2018

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

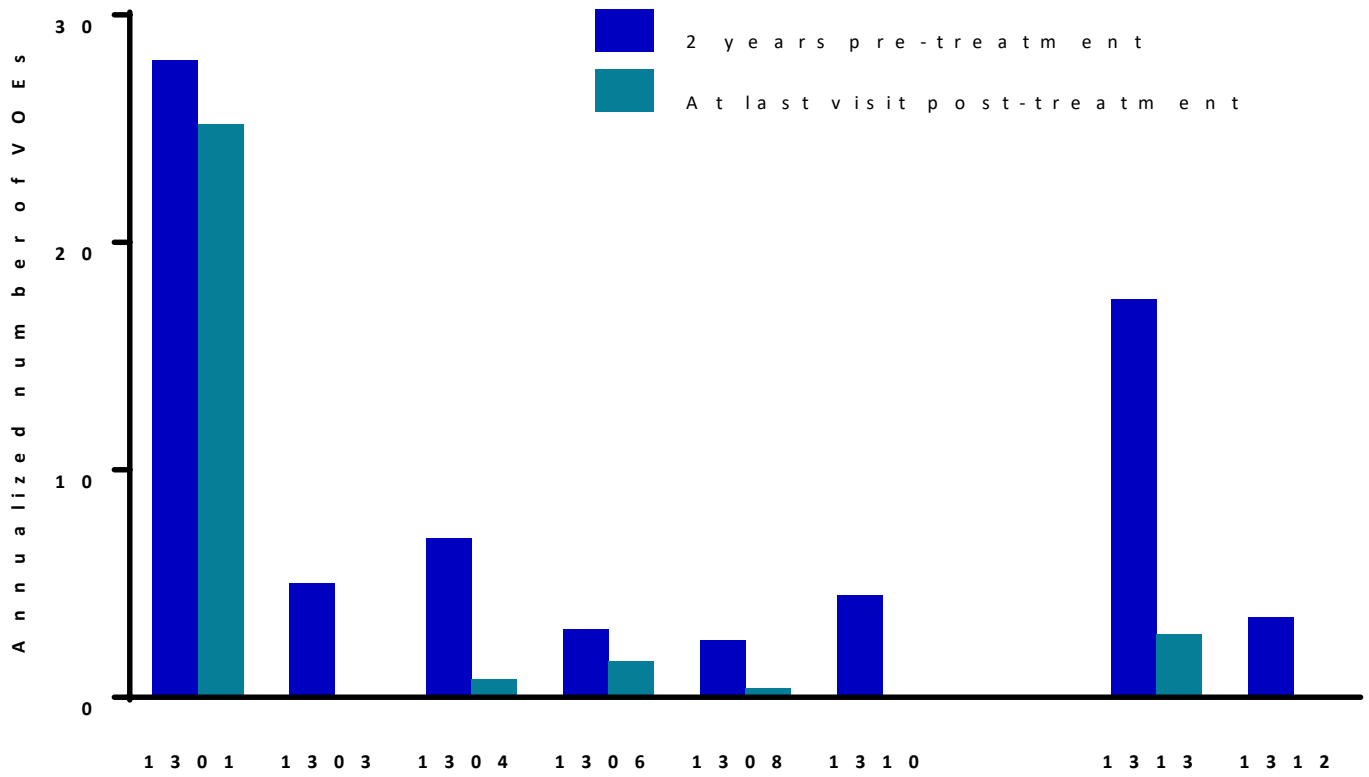
- $\beta^S$ antibody was used for intracellular staining of RBCs followed by FACS analysis
  - Controls showed distinct $\beta^S$ distributions, with SS > AS > AA
- Results in 2 patients 9 and 15 months post treatment show decreased $\beta^S$ in nearly all RBCs, even less than AS (trait)
  - Most non-$\beta^S$ globin in these samples is $\beta^{A\text{-}T87Q}$
  - Patients stopped RBC transfusion and HbF < 2.5% of total globin chains




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

Data as of September 14, 2018

# HGB-206 Groups A and B: All patients have decreased rate of annualized VOEs post-transplant




| | 1301 | 1303 | 1304 | 1306 | 1308 | 1310 | 1313 | 1312 |
|---|---|---|---|---|---|---|---|---|
| % Decrease from baseline | 10 | 100 | 89 | 46 | 84 | 100 | 84 | 100 |
| Last study visit (Month) | 36 | 36 | 30 | 30 | 30 | 30 | 18 | 15 |

- **Patient 1309 with stroke before enrollment stopped RBC transfusions and had no stroke post-infusion**

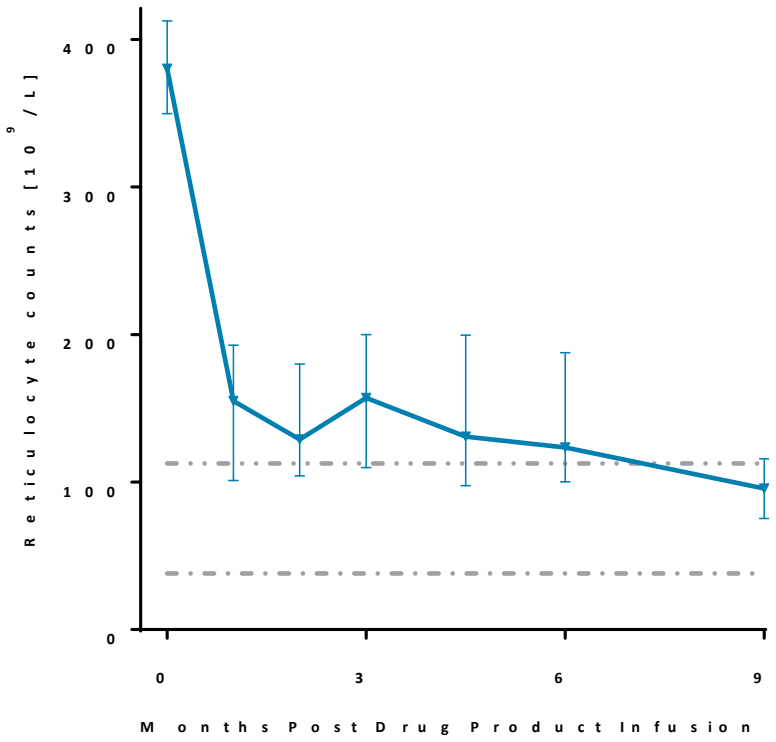
VOEs include VOCs or ACS, with VOC described as pain episode lasting ≥ 2 hours and requiring care at medical facility, and ACS defined as an acute event with pneumonia-like symptoms and the presence of a new pulmonary infiltrate

ACS, acute chest syndrome; RBC, red blood cell; VOCs, vaso-occlusive crises; VOEs, vaso-occlusive events

Data as of September 14, 2018

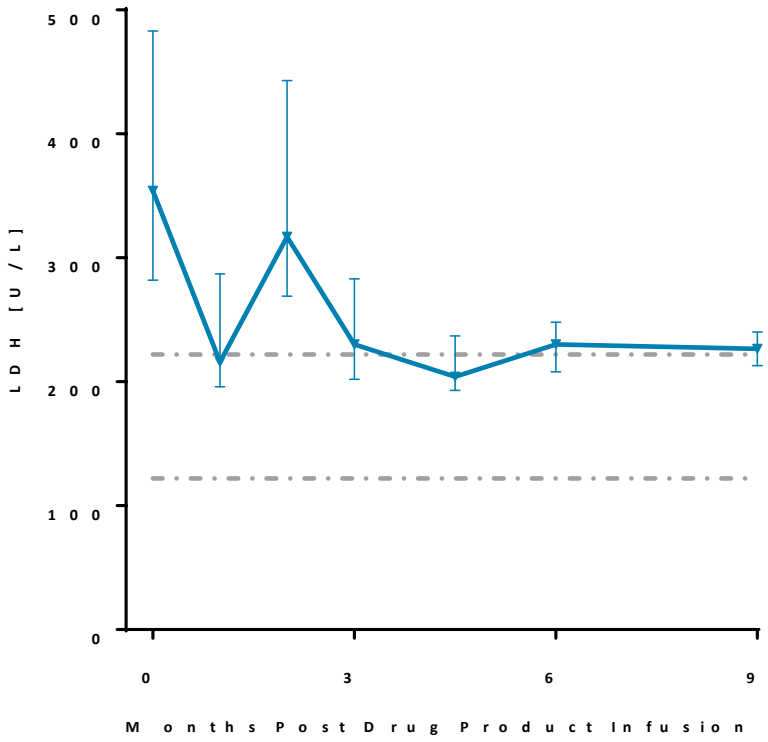
# HGB-206 Group C: Decreased hemolysis following LentiGlobin gene therapy

## Reticulocyte Counts



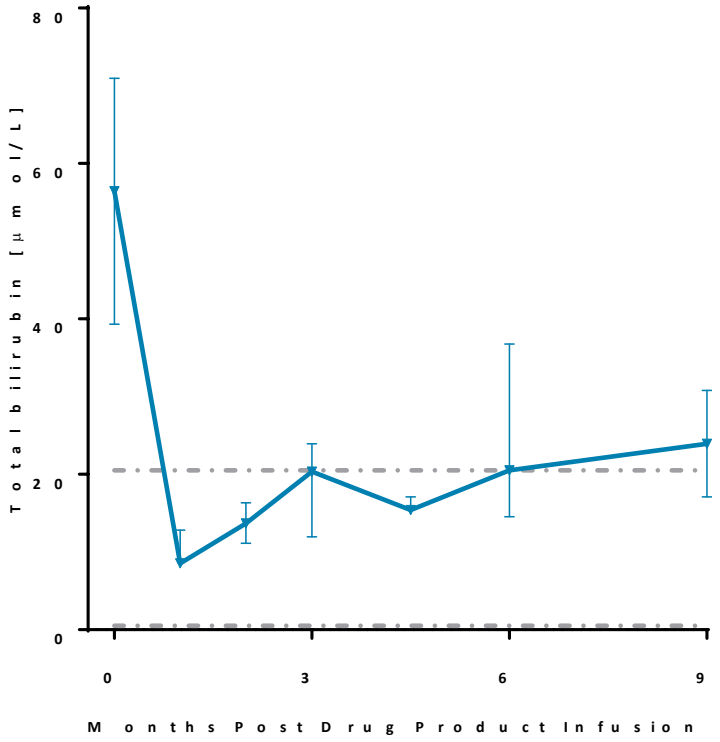

N 4 7 7 7 6 4 2

## Lactate Dehydrogenase




7 7 7 7 6 3 2

## Total Bilirubin




9 8 8 7 6 4 2

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

LDH, lactate dehydrogenase

# Summary

- Even modest $HbA^{T87Q}$ levels (0.7-2.8 g/dL at last visit) appear to have clinical effect (decreased VOE frequency)
- Refined manufacturing and other protocol modifications have improved results:
  - **Group B patients had increased $HbA^{T87Q}$ levels (3.4-6.5 g/dL) and total Hb levels associated with 84-100% reduction in VOE frequency**
  - **Group C demonstrates robust $HbA^{T87Q}$ production of 4.8-8.8 g/dL at ≥ 6 months that equals or exceeds HbS levels**
    - Safety and feasibility of plerixafor mobilization and apheresis in SCD was shown
    - Hb of 9.9-13.7 g/dL at last visit without RBC transfusion
    - Decreased hemolysis after LentiGlobin gene therapy
- Safety profile of LentiGlobin gene therapy for severe SCD is consistent with myeloablative conditioning and underlying SCD
  - One case of MDS reported, not related to LentiGlobin gene therapy
- Exploratory translational assay suggests pancellular expression of gene therapy-derived Hb
- Protocol amended to further evaluate the clinical impact of LentiGlobin gene therapy in SCD

Hb, hemoglobin; MDS, myelodysplastic syndrome; RBC, red blood cell; VOE, vaso-occlusive event

# Updates to HGB-206: An open-label, multicenter phase 1/2 study of LentiGlobin 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 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

# Thank you to the study participants and their families

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