EHA 2018 Abstract S836

Recent progress in gene therapy for severe sickle cell disease: Updated interim results from a phase 1 clinical study of LentiGlobin gene therapy

Julie Kanter, Alexis Thompson, Markus Mapara, Mark Walters, Janet Kwiatkowski, Lakshmanan Krishnamurti, Manfred Schmidt, Alexandra Miller, Francis Pierciey, Jean-Antoine Ribeil, Weiliang Shi, Mohammed Asmal, John Tisdale

Disclosure of affiliations

- Advisory Board: AstraZeneca, bluebird bio, Novartis, NHLBI, ASH
- Research Funding: GBT, Sancillo, Apopharma, Pfizer, bluebird bio, Novartis, NHLBI

HGB-206: study of LentiGlobin gene therapy for severe sickle cell disease

HGB-206

Key Enrollment Criteria

- 18+ years of age
- History of symptomatic SCD
- Adequate organ function
- No previous HSCT or gene therapy

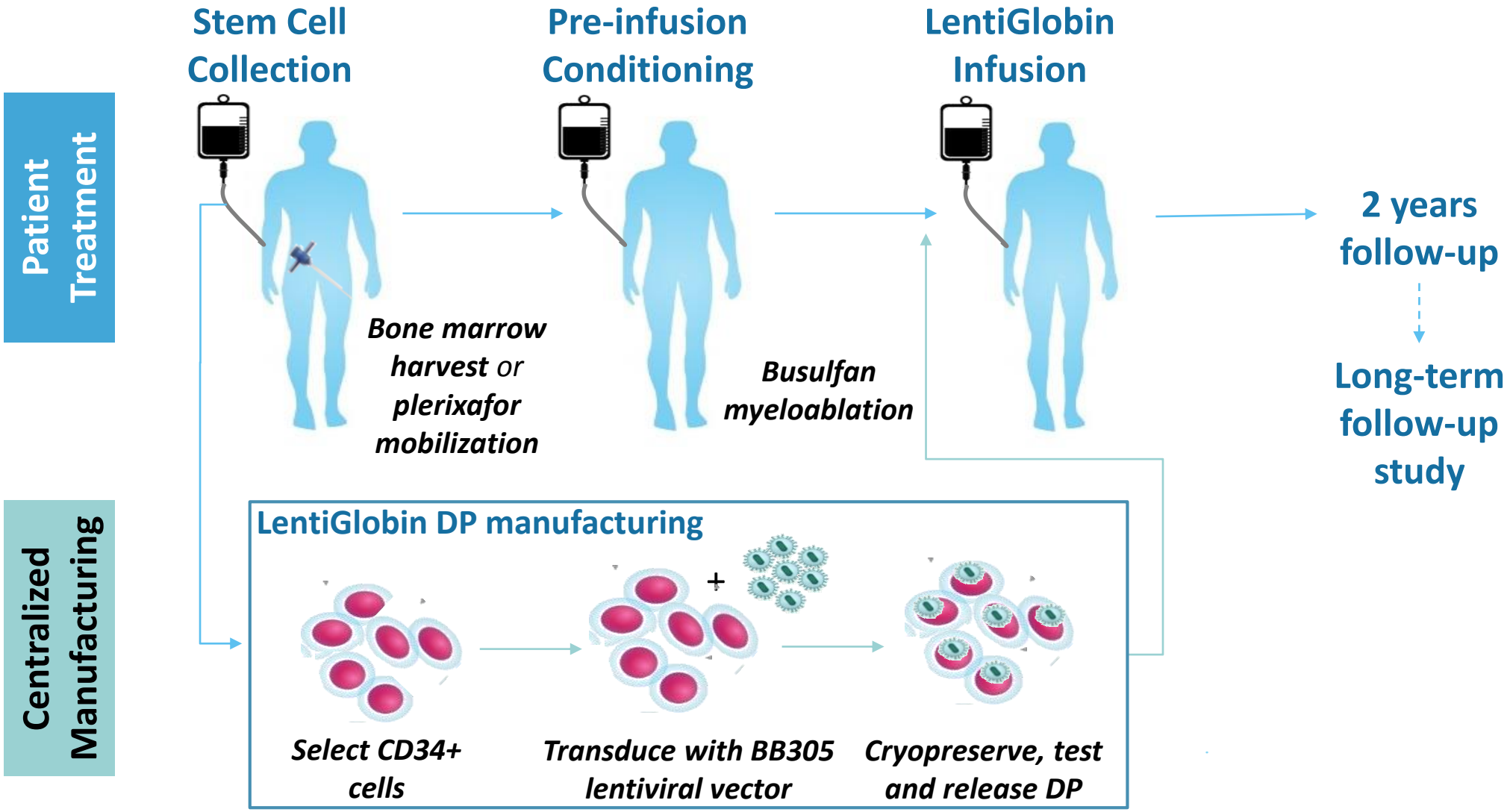
Target enrollment: up to 29

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

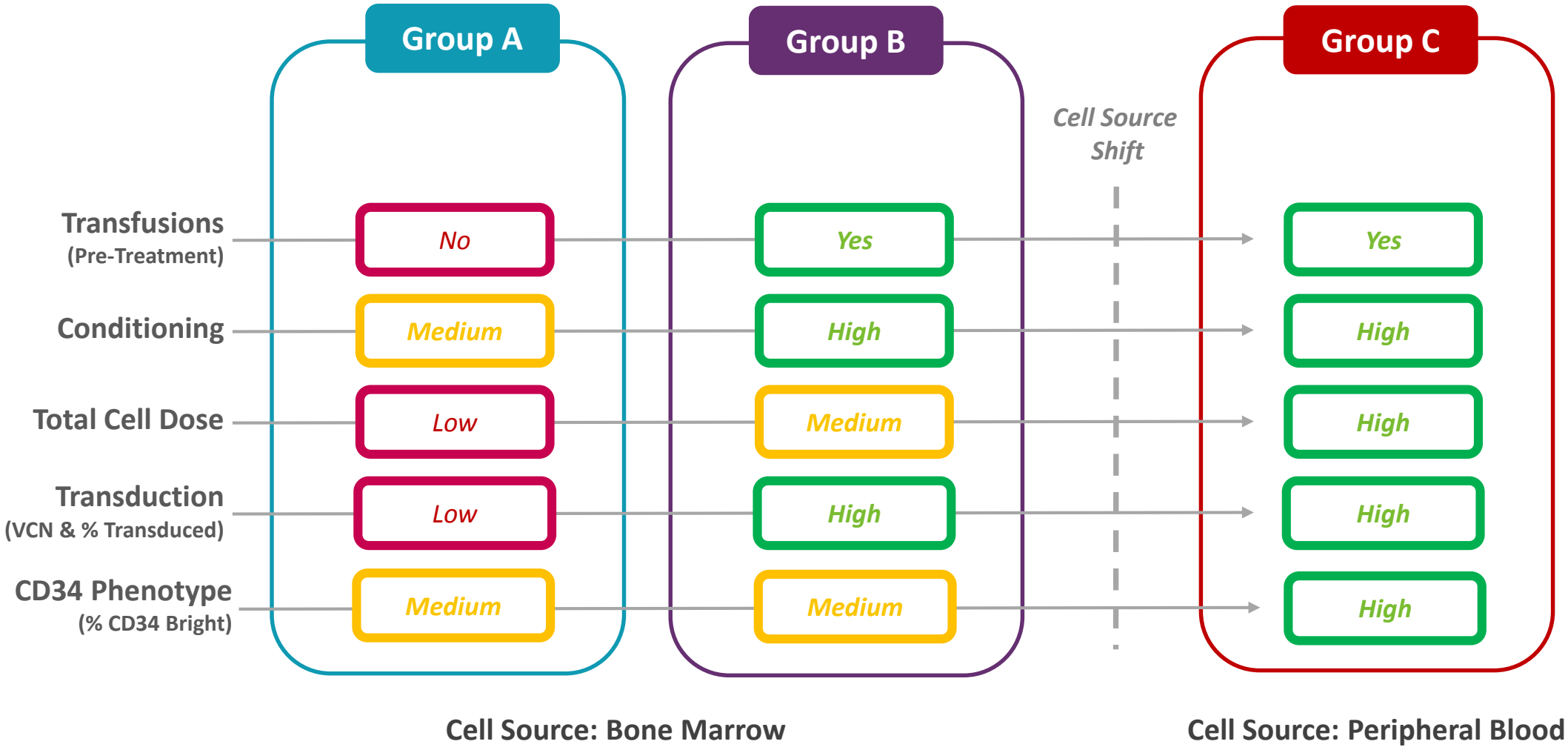
Study initiated August 2014

HGB-206: An open-label, multicenter phase 1 study of LentiGlobin gene therapy for severe sickle cell disease

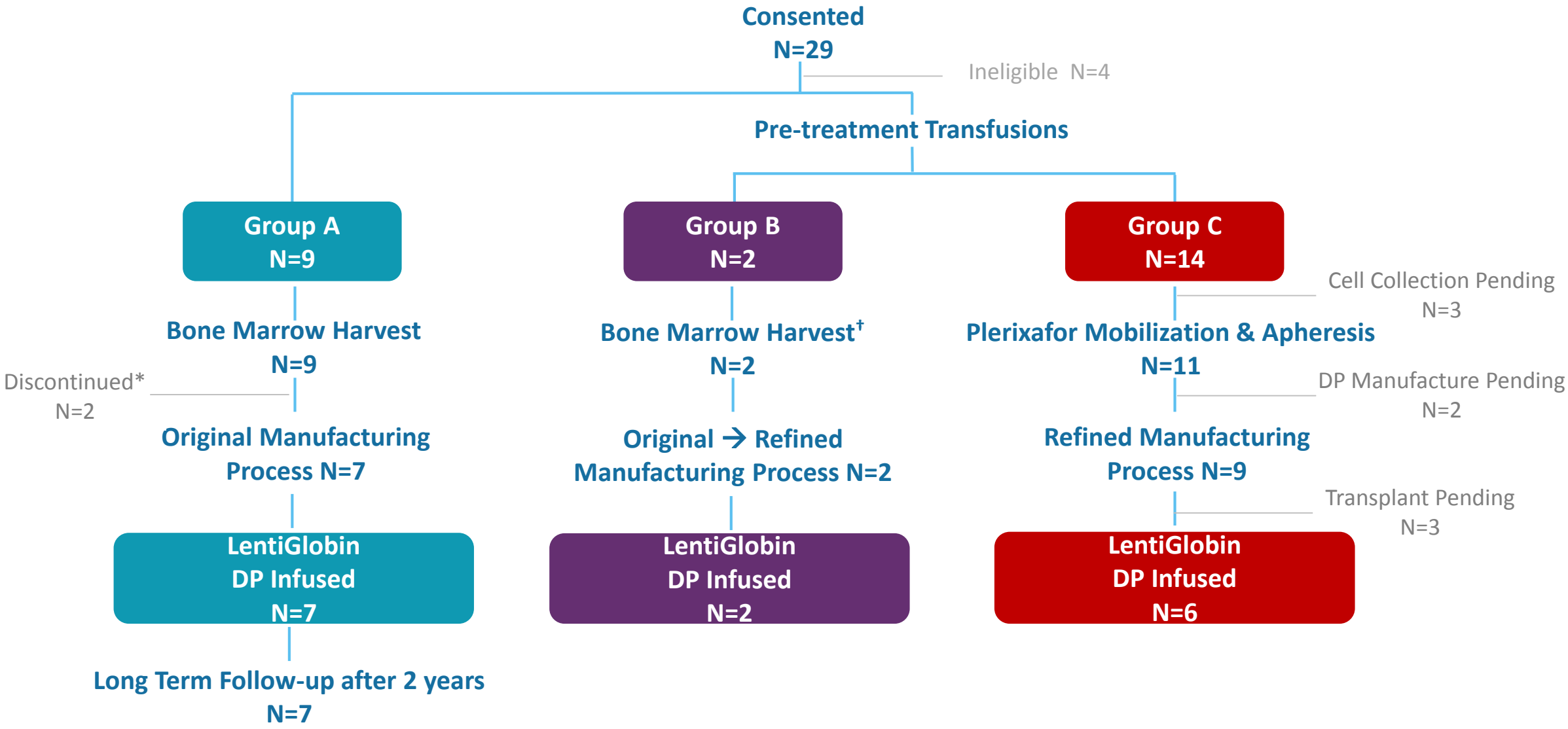


DP, drug product

Evolution of HGB-206: Protocol and DP manufacturing changes promise improved outcomes



HGB 206: Study disposition



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

Data as of May 15, 2018

Results

HGB-206: Patient characteristics

N=22 patients who started cell collection

Parameter	Group A N=9	Group B N=2	Group C N=11
Age at consent median (min – max), years	**26** (18 – 43)	**24.5** (22 – 27)	**25** (18 – 35)
Gender	**2 F 7 M**	**0 F 2 M**	**5 F 6 M**
Genotype β^S/β^S	**9**	**2**	**11**
Prior SCD History			
Hydroxyurea use, n	**5**	**2**	**6**
Recurrent VOCs[*], n Annualized no. of events, median (min – max)	**7** **4.5** (2.0 – 27.5)	**2** **10.0** (2.5 – 17.5)	**6** **7.5** (4.0 – 14.0)
ACS[†], n Annualized no. of events, median (min – max)	**1** **1**	**1** **1**	**2** **1** (1 – 1)
Any history of stroke, n	**2**	**0**	**3**
Regular pRBC transfusions before study entry, n	**1**	**0**	**7**
TRJV >2.5 m/s, n	**1**	**0**	**0**

* ≥2 events/year in preceding 2 years; [†] ≥2 episodes in preceding 2 years, with at least one episode in the past year or in the year prior to the initiation of a regular transfusion program

ACS, acute chest syndrome; VOC, vaso-occlusive crisis; pRBC, packed red blood cell; TRJV, tricuspid regurgitant jet velocity

Data as of May 15, 2018

HGB-206: Treatment characteristics

N=15 DP infused patients

Parameter	Group A N=7 Median (min – max)	Group B N=2 Median (min – max)	Group C N=6 Median (min – max)
No. of bone marrow harvests	**2** (1 – 4)	**2.5** (2 – 3)	NA
No. of mobilization cycles	NA	**1**^	**1** (1 – 2)
Busulfan AUC, µM*min†	**4747** (4084 – 5290)	**5017**, NR	**4768** (4608 – 5182)
Follow-up, months	**24.2** (22.8 – 32.9)	**11.4** (8.5 – 14.3)	**3.0** (1.2 – 6.0)
Neutrophil engraftment, days‡	**22** (17 – 29)	**26** (23 – 28)	**19** (18 – 20)
Platelet engraftment, days#	**56** (29 – 63)	**46** (31 – 61)	**28** (12 – 64)¶
Duration of hospitalization, days§	**37** (29 – 54)	**41** (36 – 46)	**34** (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; ^For research purposes; ¶Based on data from 4 patients; NA = not applicable; NR = not recorded.

HGB-206: Safety associated with cell collections

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

Grade ≥ 3 AEs in 11† patients who had BMH	n
Procedural pain[1]	6
Anemia	2
Sickle cell anemia with crisis[2]	2
Lymphocyte count increased	1

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

- In 25 plerixafor mobilizations / apheresis days in 12‡ patients, 5 grade ≥3 AEs were reported in 3 patients

Grade ≥ 3 AEs in 12‡ patients who had plerixafor mobilizations / apheresis	n
Sickle cell anemia with crisis[1]	3
Hypomagnesaemia	1
Non-cardiac chest pain	1

[1] Considered serious; were consistent with patients' histories of VOEs. Patients were hospitalized, or hospitalization was prolonged, for standard management. All 3 patients recovered without sequelae

*Patient could have experienced same AE more than once; †9 Group A and 2 Group B; ‡1 Group B and 11 Group C

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

Data as of May 15, 2018

HGB-206: Safety profile post DP infusion

N=15 DP infused patients

Non-hematologic* grade ≥3 AEs Post DP infusion reported in ≥2 patients	**n**
Stomatitis	11
Febrile neutropenia	10
Sickle cell anemia with crisis	5
Pharyngeal inflammation	4
Bacteremia	2
Dyspnoea	2
Epistaxis	2
Non-cardiac chest pain	2
Pyrexia	2

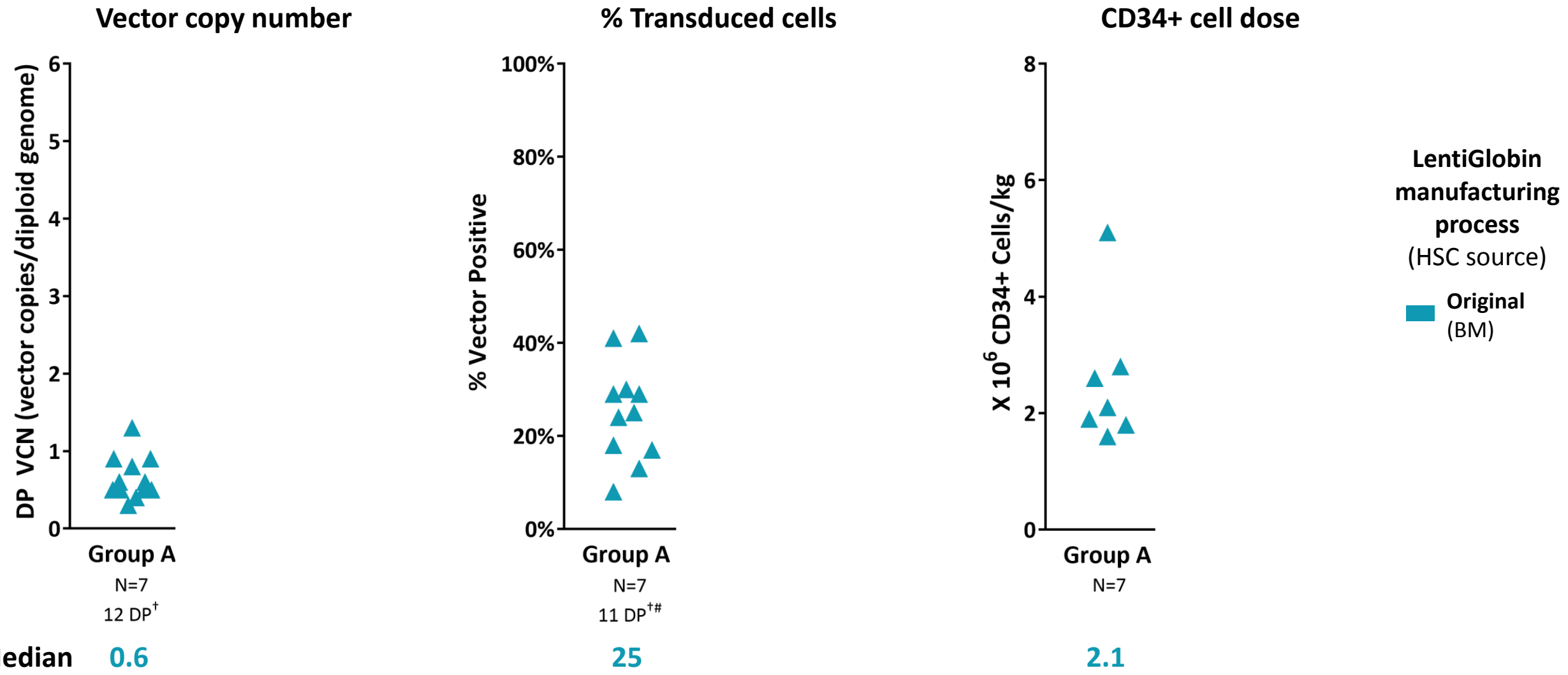
- Grade ≥3 hematologic AEs were generally consistent with myeloablative busulfan conditioning
- SAEs reported in 11 patients, with sickle cell anemia with crisis (n = 5) as most common
- 1 AE (hot flush, grade 1) considered possibly related to DP
- **No cases of VOD observed to date**
- **No vector-mediated RCL detected to date**
- **Continued highly polyclonal repopulation**

*Hematologic AEs commonly observed post-transplant have been excluded

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

Data as of May 15, 2018

Refinements to manufacturing and cell harvest lead to improved drug product characteristics



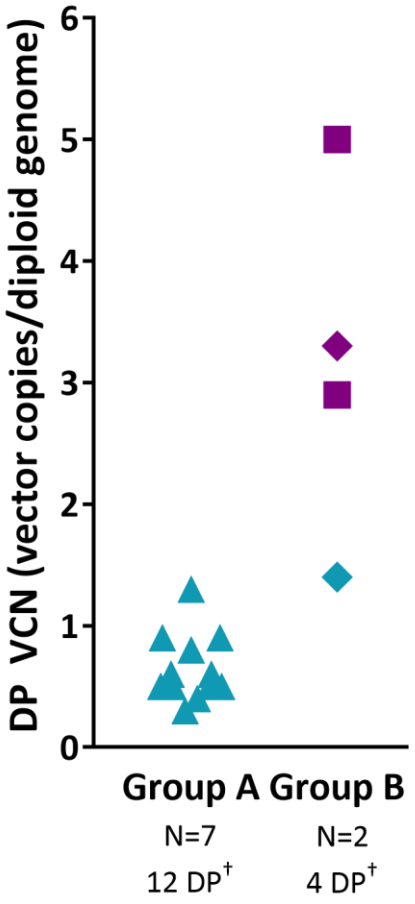
† Number of DP exceeds number of patients since some patients were harvested or mobilized more than once; # % Transduced cells not available for 1 DP at time of analyses.

BM, bone marrow; HSC, hematopoietic stem cell; PB, peripheral blood

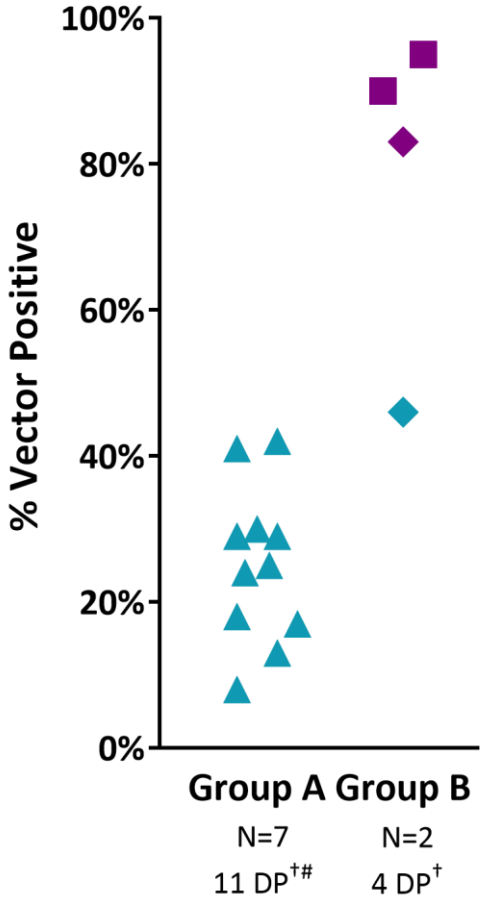
Data as of May 15, 2018

Refinements to manufacturing and cell harvest lead to improved drug product characteristics

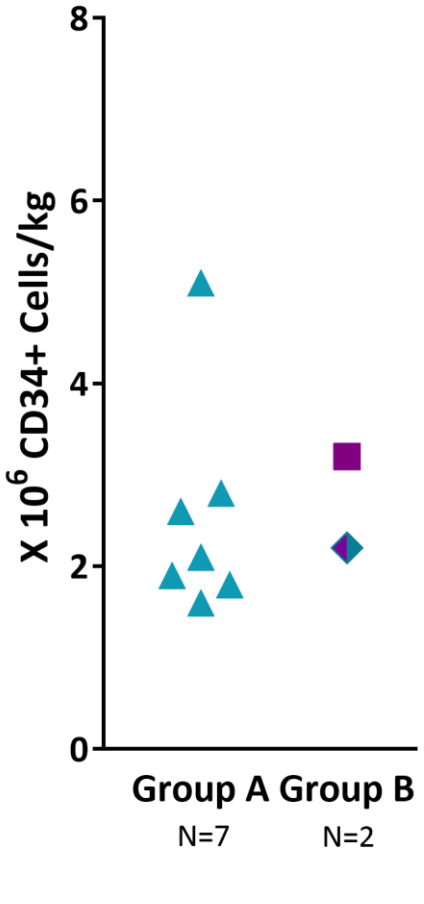
Vector copy number



% Transduced cells



CD34+ cell dose



LentiGlobin manufacturing process
(HSC source)

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

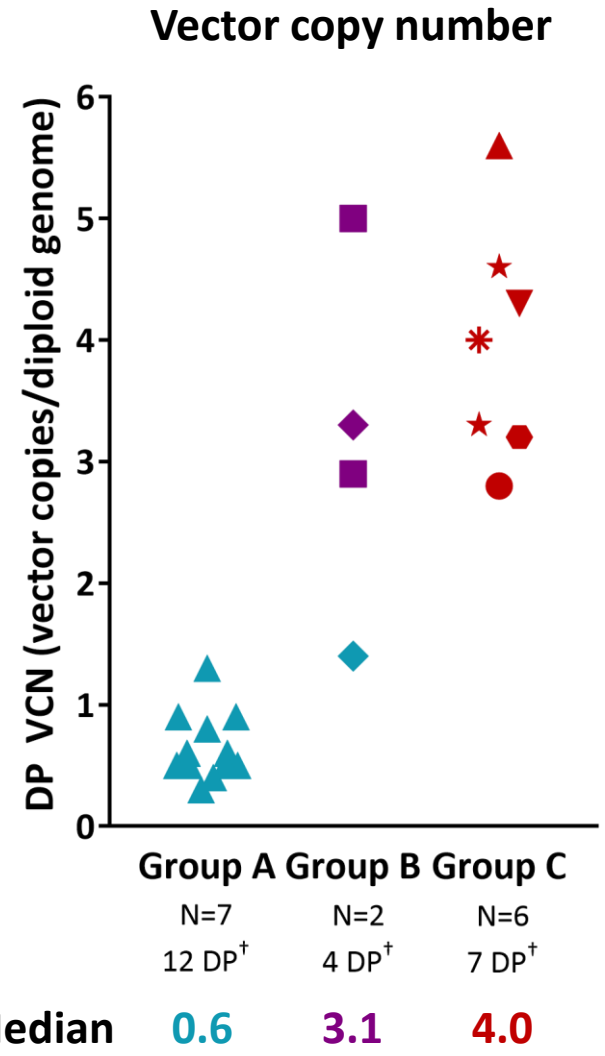
	Group A	Group B
Median	0.6	3.1
Median	25	87
Median	2.1	2.7

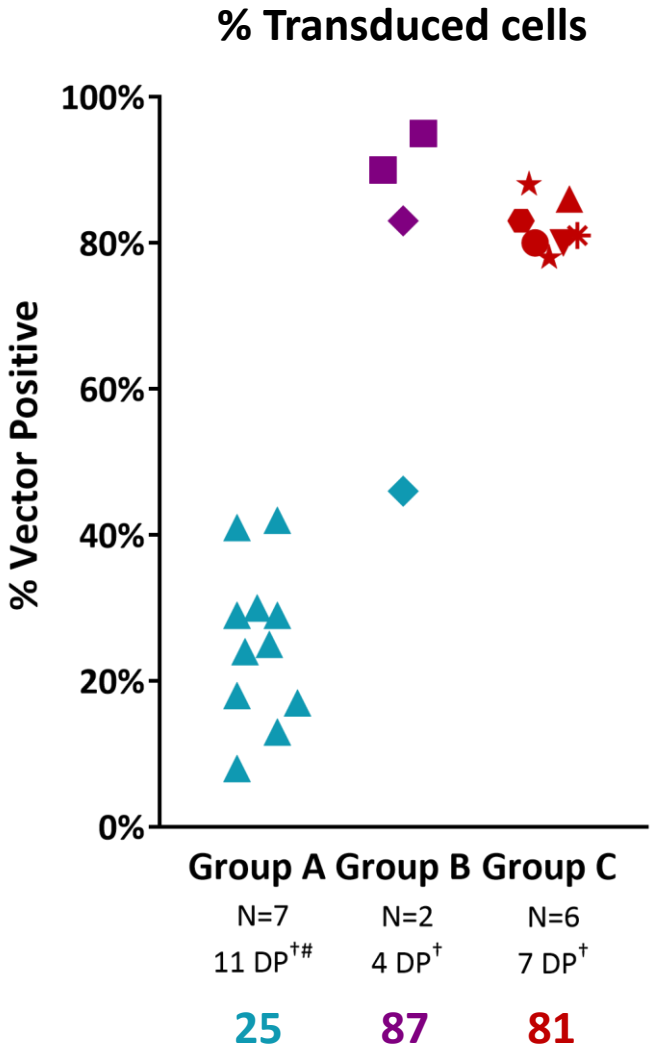
† Number of DP exceeds number of patients since some patients were harvested or mobilized more than once; # % Transduced cells not available for 1 DP at time of analyses.

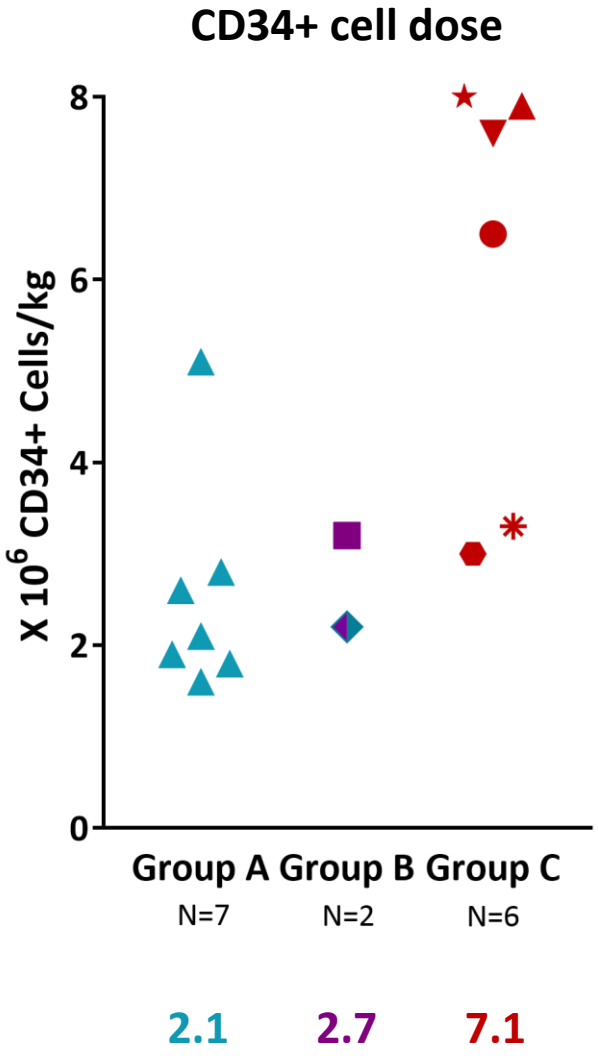
BM, bone marrow; HSC, hematopoietic stem cell; PB, peripheral blood

Data as of May 15, 2018

Refinements to manufacturing and cell harvest lead to improved drug product characteristics







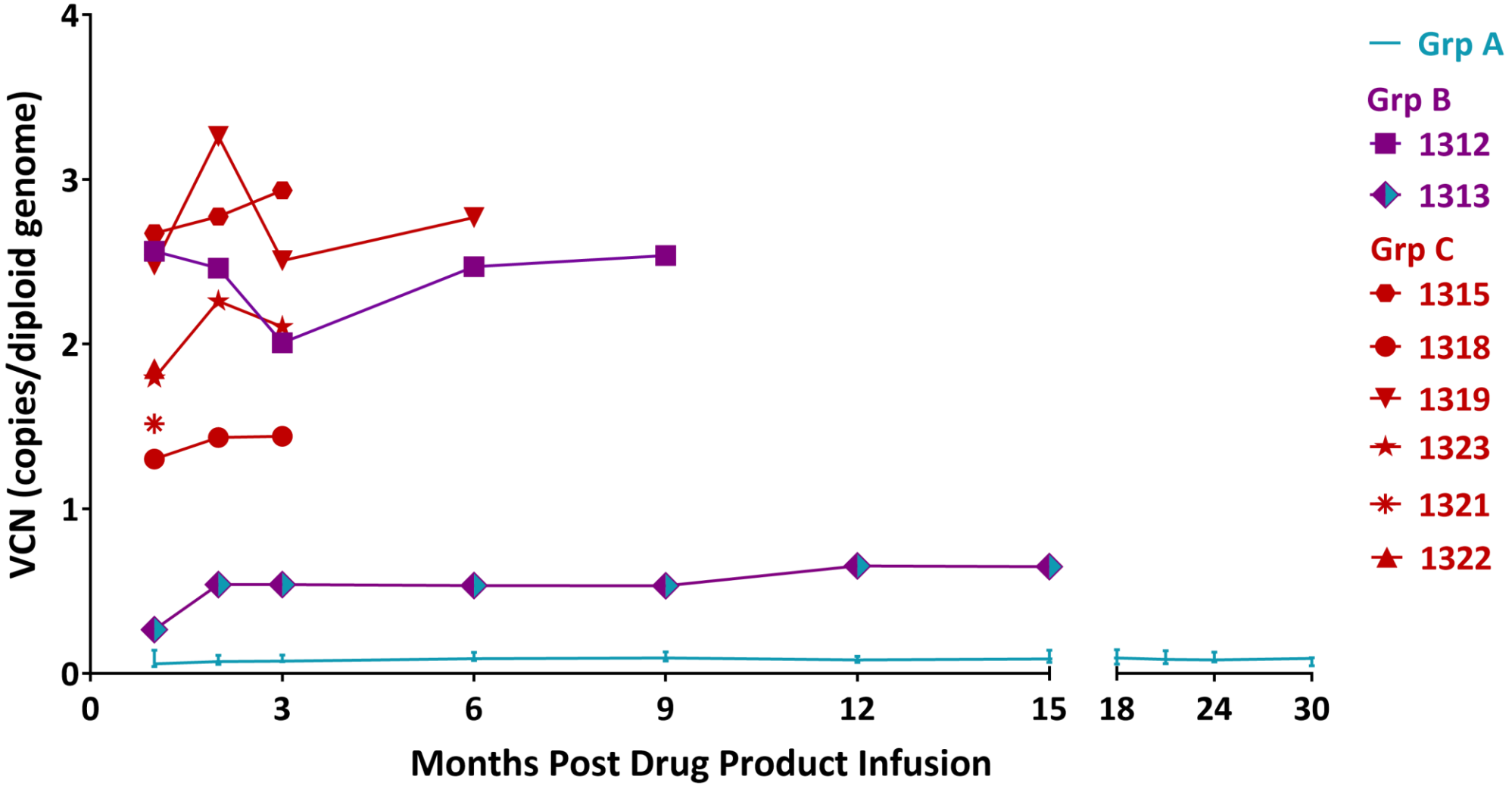
LentiGlobin manufacturing process
(HSC source)

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

† 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.

BM, bone marrow; HSC, hematopoietic stem cell; PB, peripheral blood

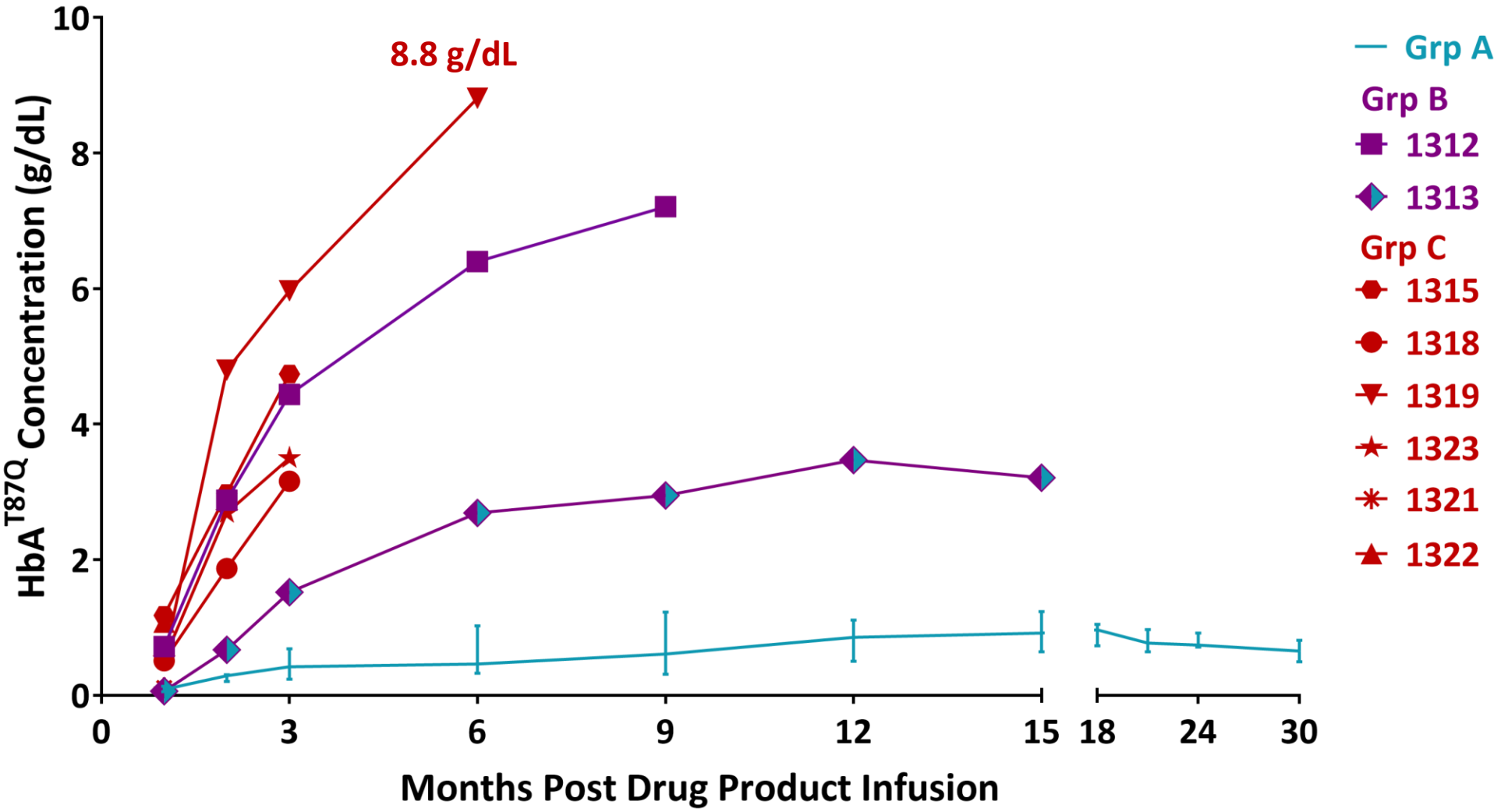
Peripheral blood VCN is higher in patients in Group B and C



For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 30 study visit (N=3)

Data as of May 15, 2018

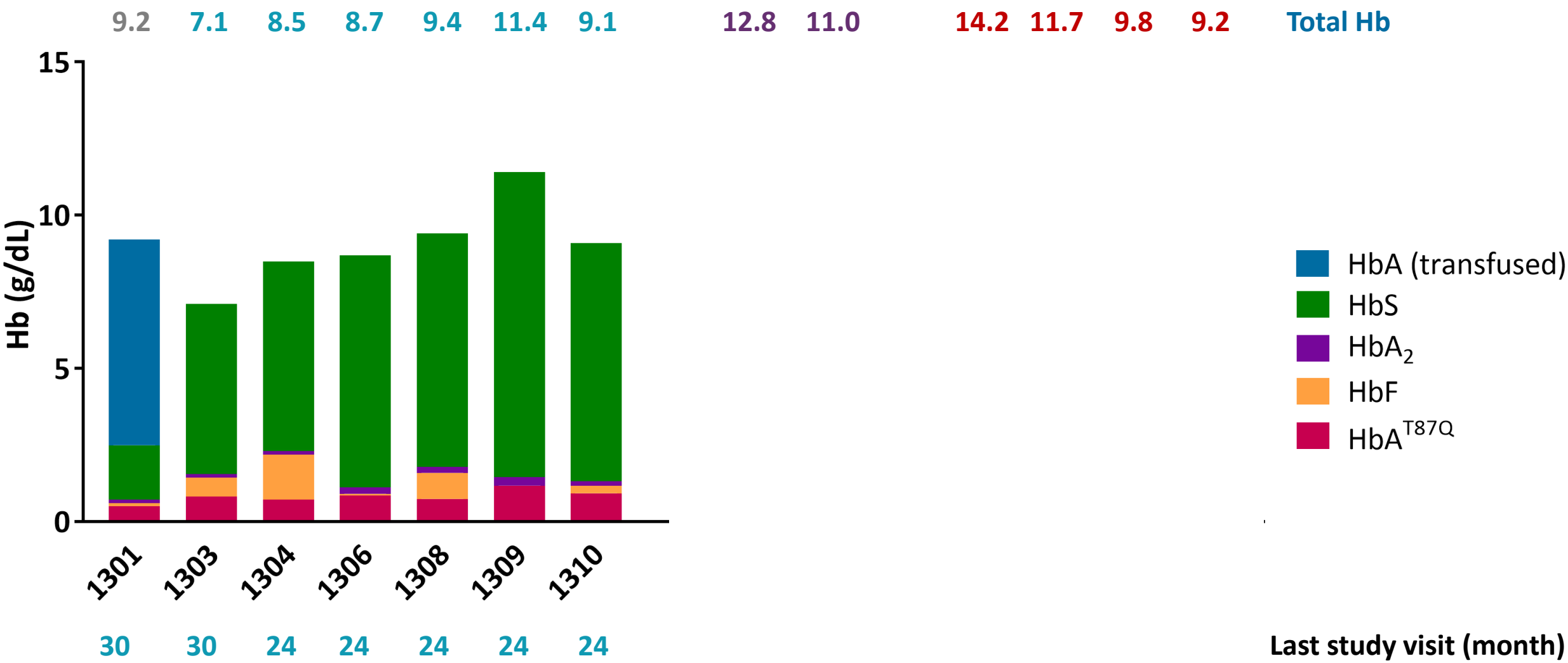
Patients in Group B and C demonstrate higher HbA^{T87Q} production



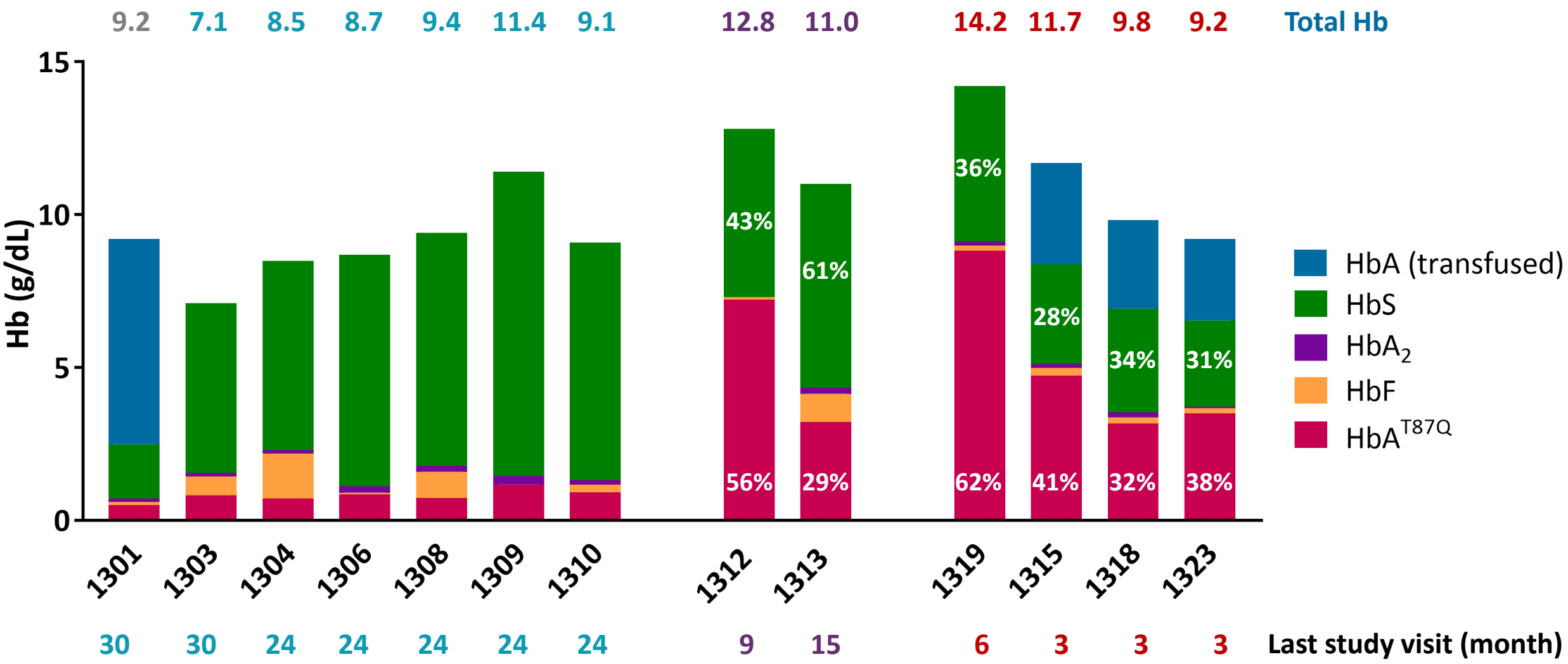
For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 30 study visit (N=2)

Data as of May 15, 2018

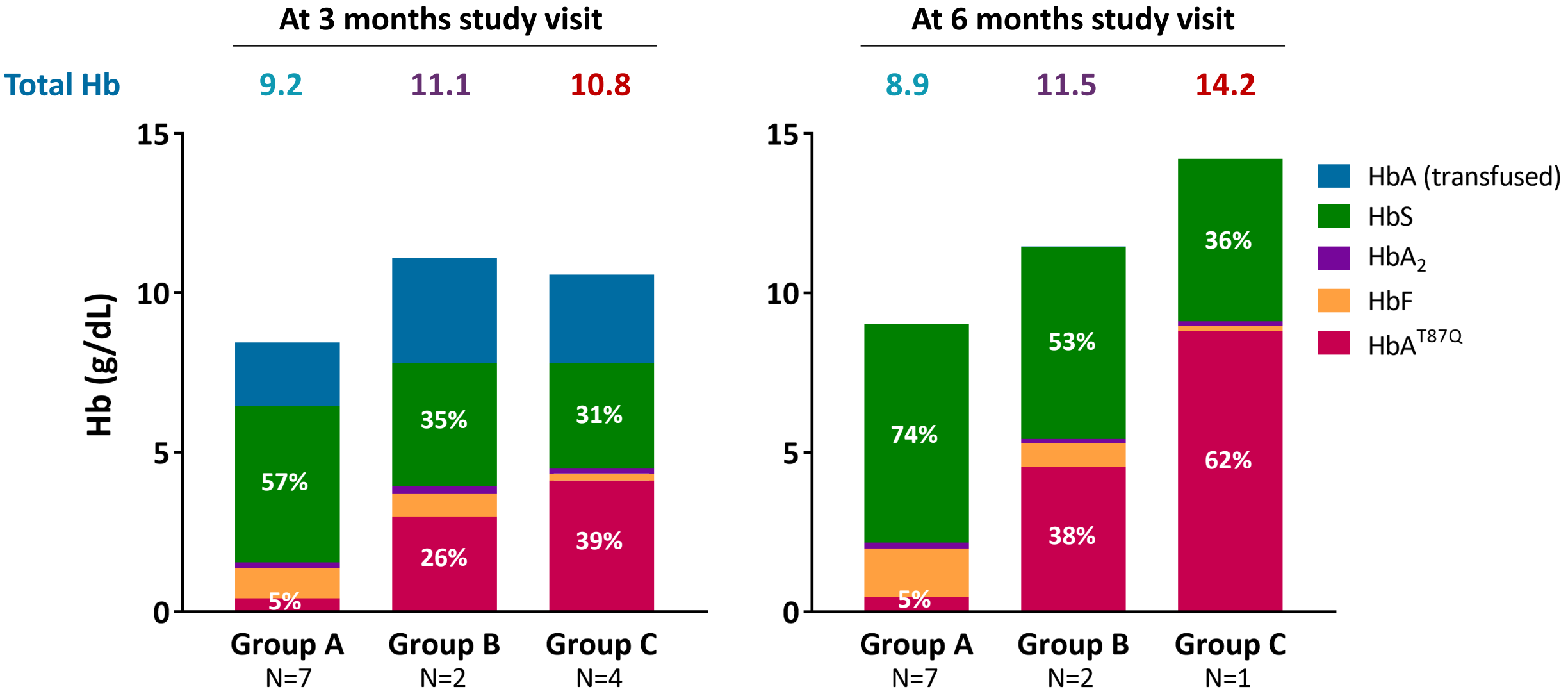
Vector-derived hemoglobin in treated patients



Vector-derived hemoglobin in treated patients



Vector-derived hemoglobin at 3 and 6 months



Summary: Updated interim results from Phase 1 study of LentiGlobin gene therapy in patients with severe SCD

- Evolution of the HGB-206 protocol yielded improved drug product characteristics
- Patients in Group C are making 3 – 6 g/dL of HbA^{T87Q} at 3 months
- At 6 months, 1 patient in Group C is making 8.8 g/dL (62%) HbA^{T87Q} with 36% HbS and 14.2 g/dL total Hb
- Steady levels of LentiGlobin vector and HbA^{T87Q} maintained through ≥ 2 years of follow-up in initial study cohort (Group A)
- Safety profile remains consistent with myeloablative conditioning
- Study experience continues to demonstrate feasibility of plerixafor mobilization and apheresis
- Additional data and longer follow-up in Group C will establish clinical impact of higher HbA^{T87Q} levels

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
- Isaiah Somers

UCSF Benioff Children's Hospital, Oakland

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

Emory University, Atlanta

- Lakshmanan Krishnamurti
- Ashley Dulson

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

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

Columbia University Medical Center

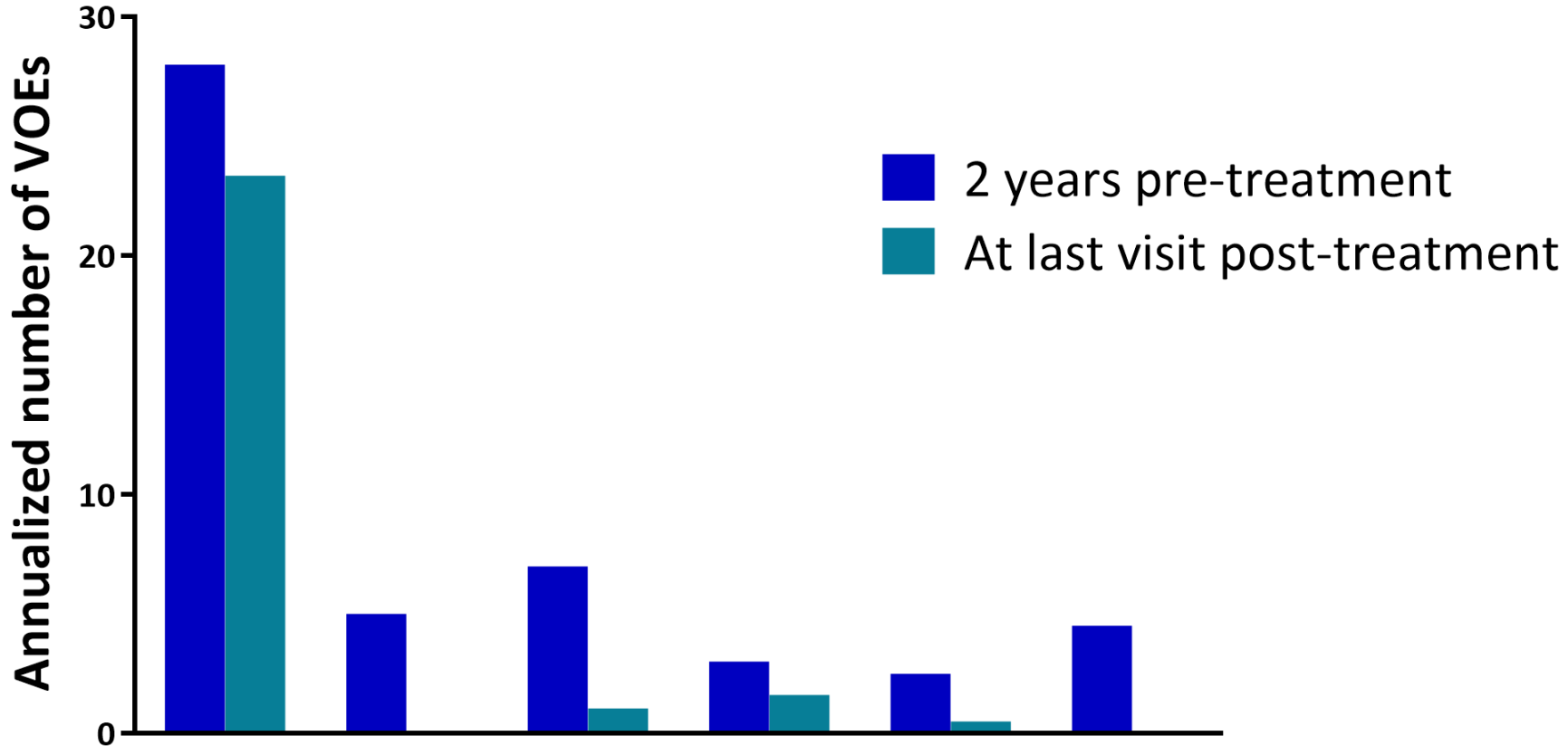
- Markus Mapara
- Monica Bhatia
- Rachel Shields

bluebird bio, Inc.

- Jean-Antoine Ribeil
- Alexandra Miller
- Weiliang Shi
- Mohammed Asmal
- Erin Whitney
- Christina White
- Ying Chen
- Iva Kronja

Back-up

Patients in Group A with >24 months follow-up have decreased rate of annualized VOEs post-transplant



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; Patient 1309 excluded from this analysis since on pre-treatment RBC transfusions

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

Data as of May 15, 2018