ASH 2017 Abstract # 527

Interim Results from a Phase 1/2 Clinical Study of LentiGlobin Gene Therapy for Severe Sickle Cell Disease

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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

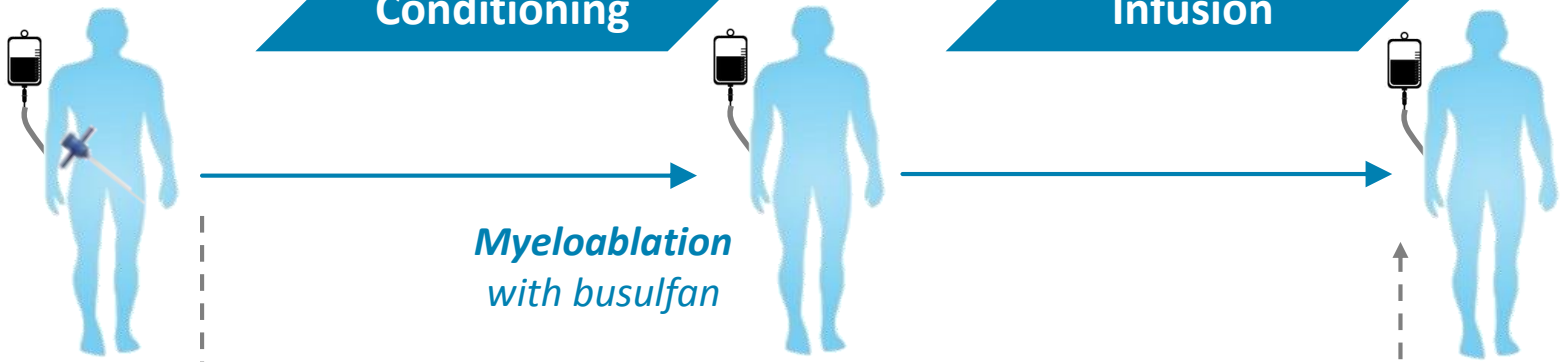
Study Objectives

- 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

HSC Collection → **Pre-infusion Conditioning** → **LentiGlobin Infusion** → **Long Term Follow-up**

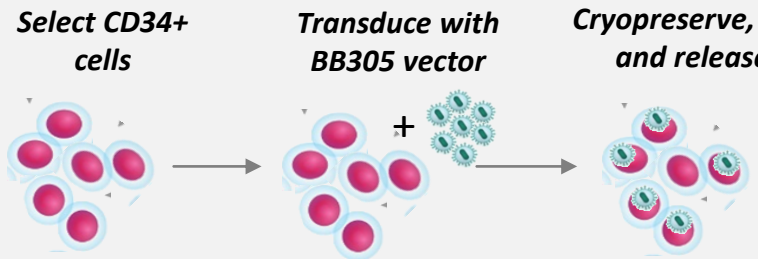


Bone marrow harvest** or **plerixafor mobilization

***Myeloablation** with busulfan*

	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

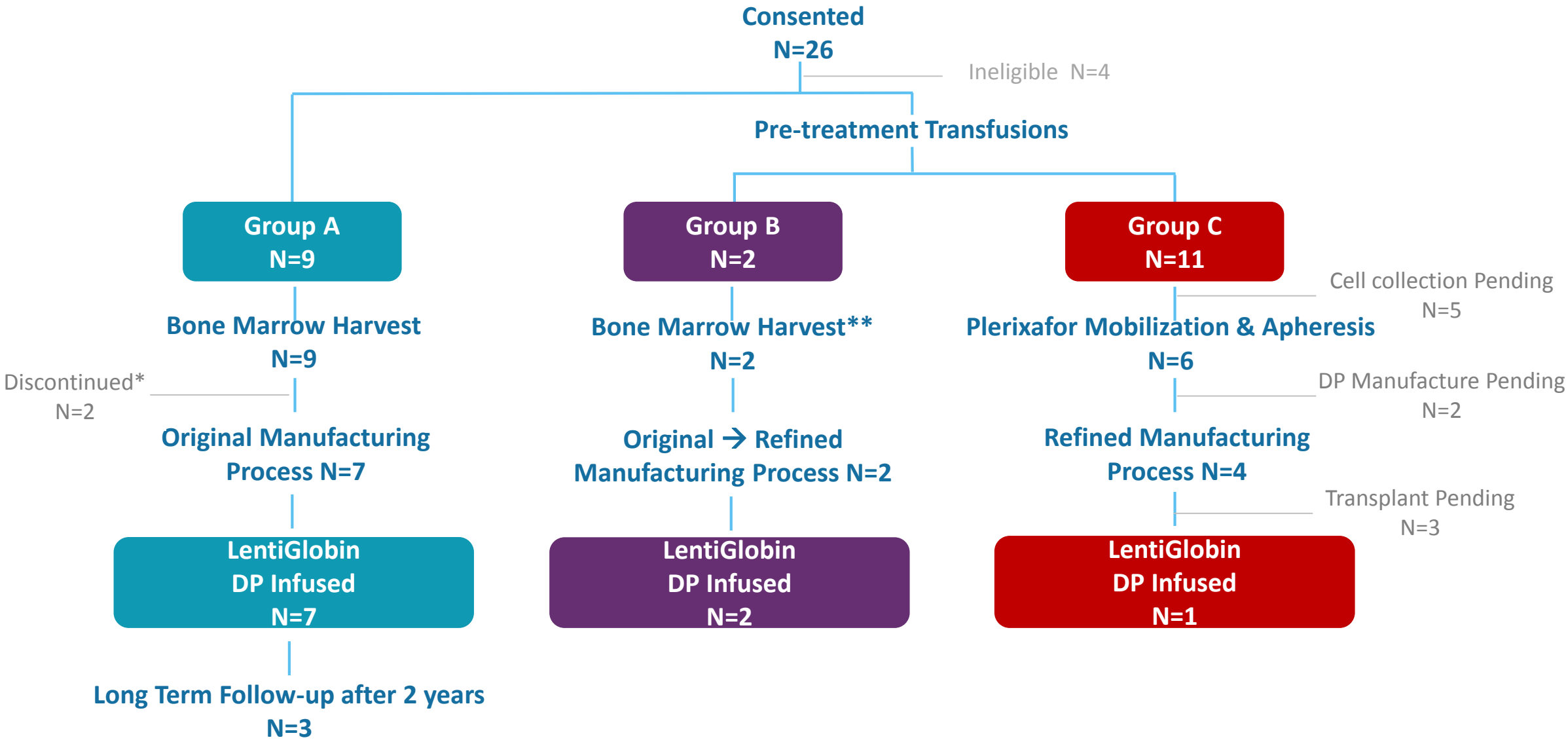
LentiGlobin DP manufacturing



[a]Protocol was modified to increase DP VCN, require pre-harvest transfusions, increase target busulfan levels, and explore the use of plerixafor for mobilization and apheresis for cell collection. [b]Patients underwent plerixafor mobilization & apheresis for exploratory analysis
BMH, bone marrow harvest; DP, drug product; HSC, hematopoietic stem cell; VCN, vector copy number.

Results

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 Nov 30, 2017

HGB-206: Patient characteristics

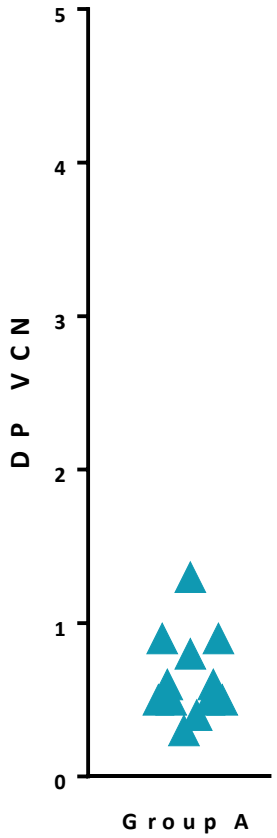
N=17 patients

Parameter		
Age at enrollment, years; median (min – max)	**26** (18 – 43)	
Gender	**5 Female, 12 Male**	
Genotype, β^S/β^S	**17** (100%)	
Follow-up, months; median (min – max)	**20.9** (0.9 – 26.7)	
Prior SCD History/Complications	**No. of Patients**	**Median (min - max)[#]**
Hydroxyurea	**11**	NA
Recurrent VOCs*	**14**	4.3 (0.5 – 27.5)
Acute chest syndrome*	**11**	0.5 (0.5 – 1)
Any history of stroke	**3**	NA
Regular pRBC transfusions prior to study entry	**4**	NA
TRJV >2.5 m/s*	**1**	NA

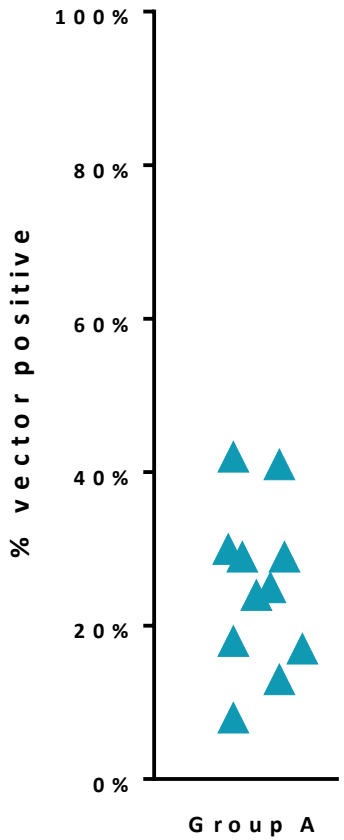
*Within 2 years prior to informed consent; [#]Median Annualized values for VOCs and ACS in patients with the event; TRJV=Tricuspid regurgitant jet velocity; NA=Not applicable

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

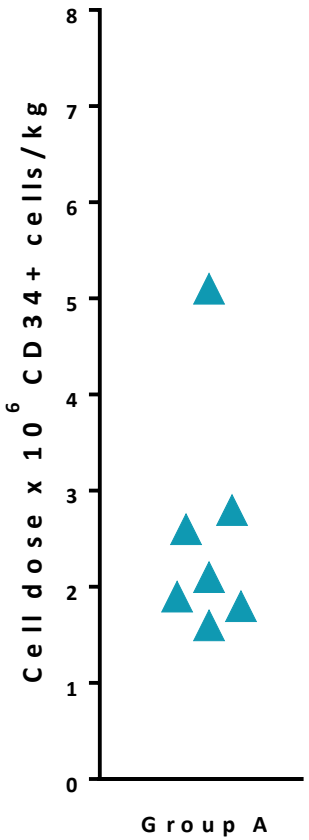
Vector Copy Number



% Transduced Cells

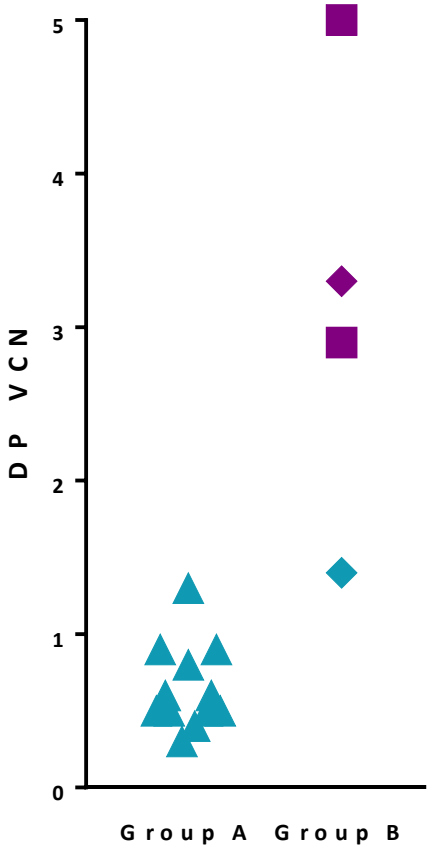


CD34+ cell count in DP

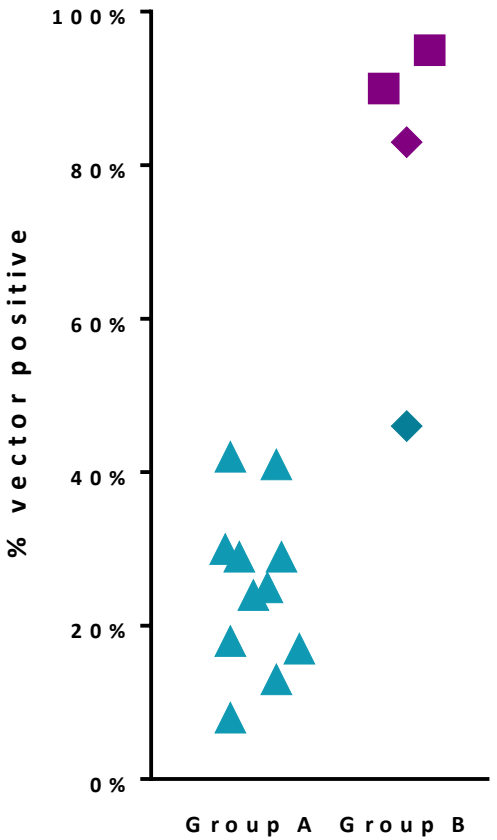


Refinements to manufacturing and cell harvest lead to improved drug product characteristics

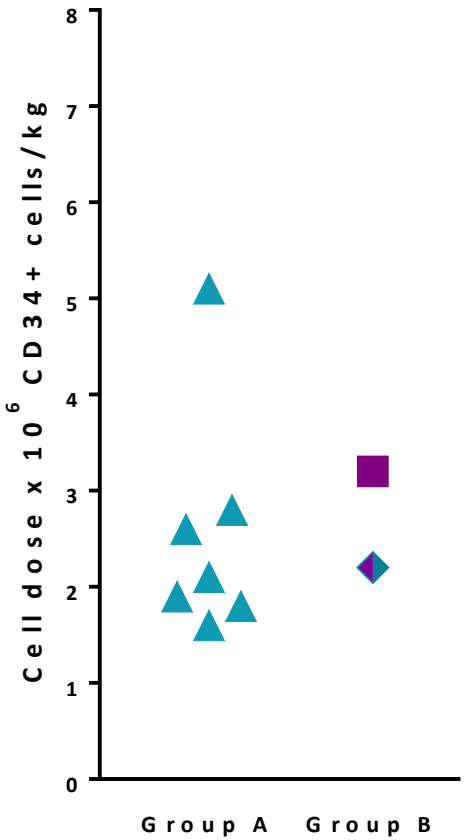
Vector Copy Number



% Transduced Cells



CD34+ cell count in DP



LentiGlobin manufacturing process

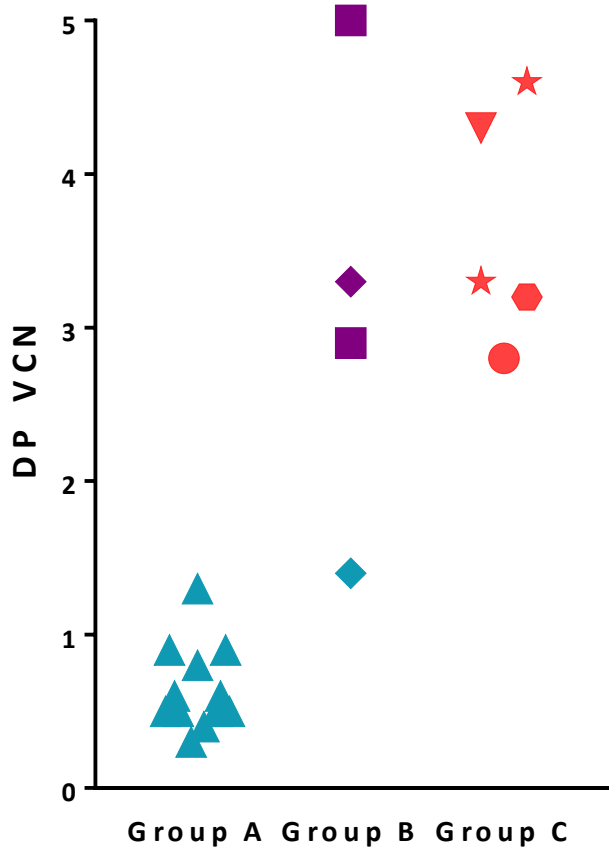
Original

Refined

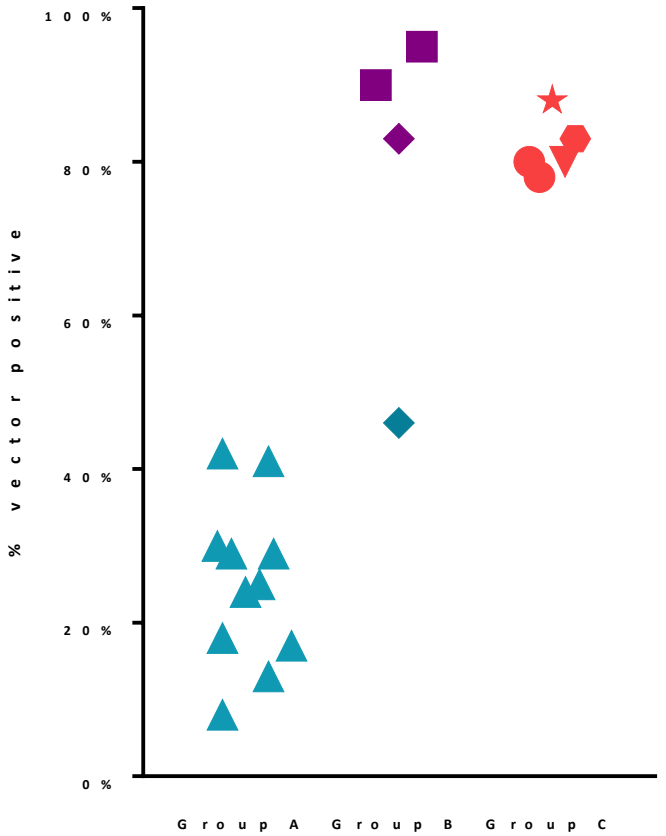
Data as of Nov 30, 2017

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

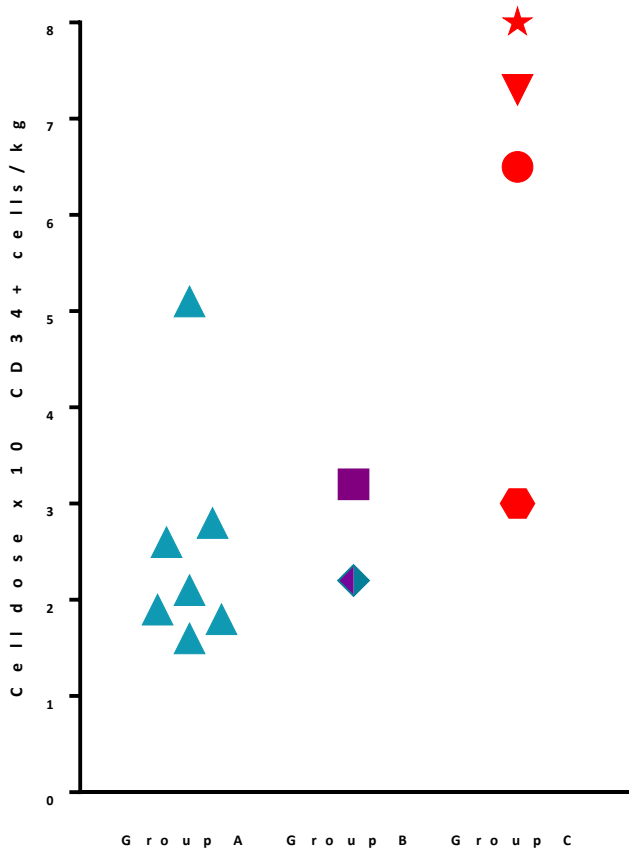
Vector Copy Number



% Transduced Cells



CD34+ cell count in DP



LentiGlobin manufacturing process

Original
Refined

Data as of Nov 30, 2017

HGB-206: Treatment and DP characteristics

N=10 transplanted patients

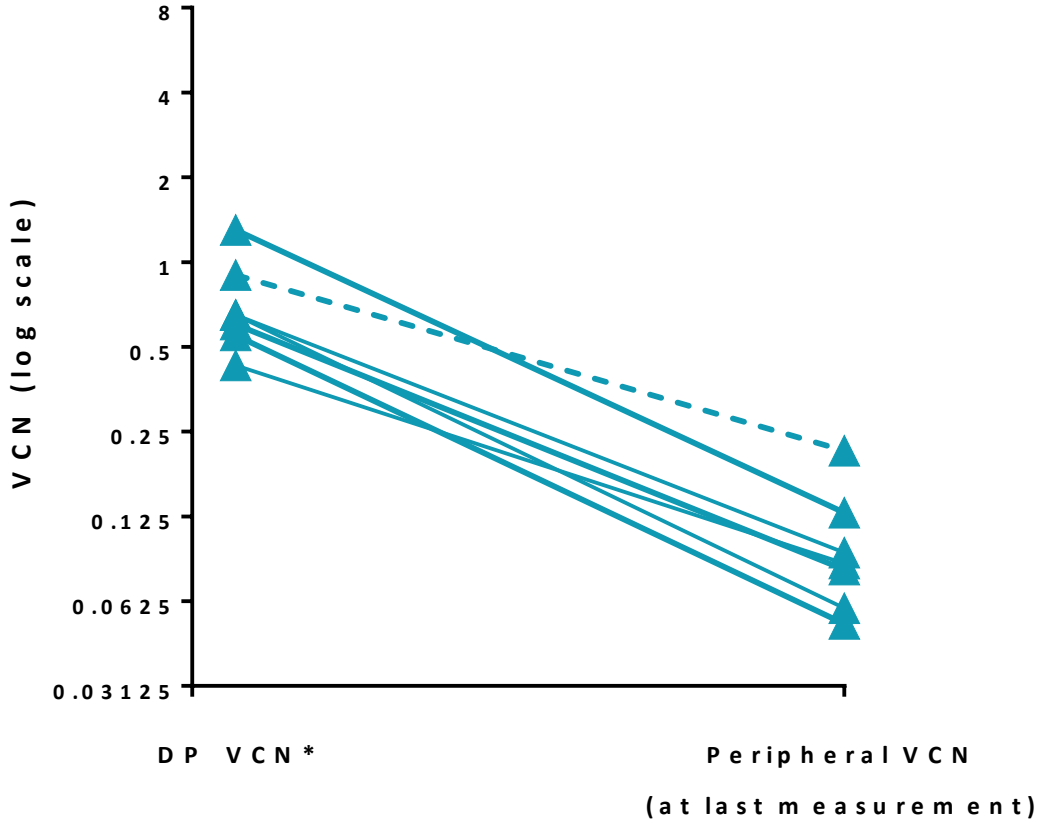
Parameter	Group A n=7 Median (min-max)	Group B n=2 Median (min-max)	Group C# n=1
No. of bone marrow harvests	**2** (1 – 4)	**2.5** (2 – 3)	NA
No. of apheresis procedures	NA	1[5]	**1**
Drug product VCN[1]	**0.6** (0.3 – 1.3)	**3.1** (1.4 – 5.0)	**4.3**
Transduced CD34+ cells, *%*	**25** (8 – 42)	**87** (46 – 95)	**80**
Drug product cell dose, *CD34+ cells x10^6/kg*	**2.1** (1.6 – 5.1)	**2.7** (2.2 – 3.2)	**7.3**
Busulfan AUC[2], *µM*min*	**4747** (4084 – 5290)	**5017**, NA	**5182**
Neutrophil engraftment, *days[3]*	**22** (17 – 29)	**26** (23 – 28)	**20**
Platelet engraftment, *days[4]*	**56** (29 – 63)	**46** (31 – 61)	Not Available

[1]VCN: number of vector copies per diploid genome. [2]Estimated average daily busulfan exposure over 4 days. [3]Absolute neutrophil count [AUC] ≥ 500 cells/µL for 3 consecutive days. [4]Unsupported platelet count ≥ 50,000/µL for 3 consecutive measures. [5]For research purposes. NA = not applicable

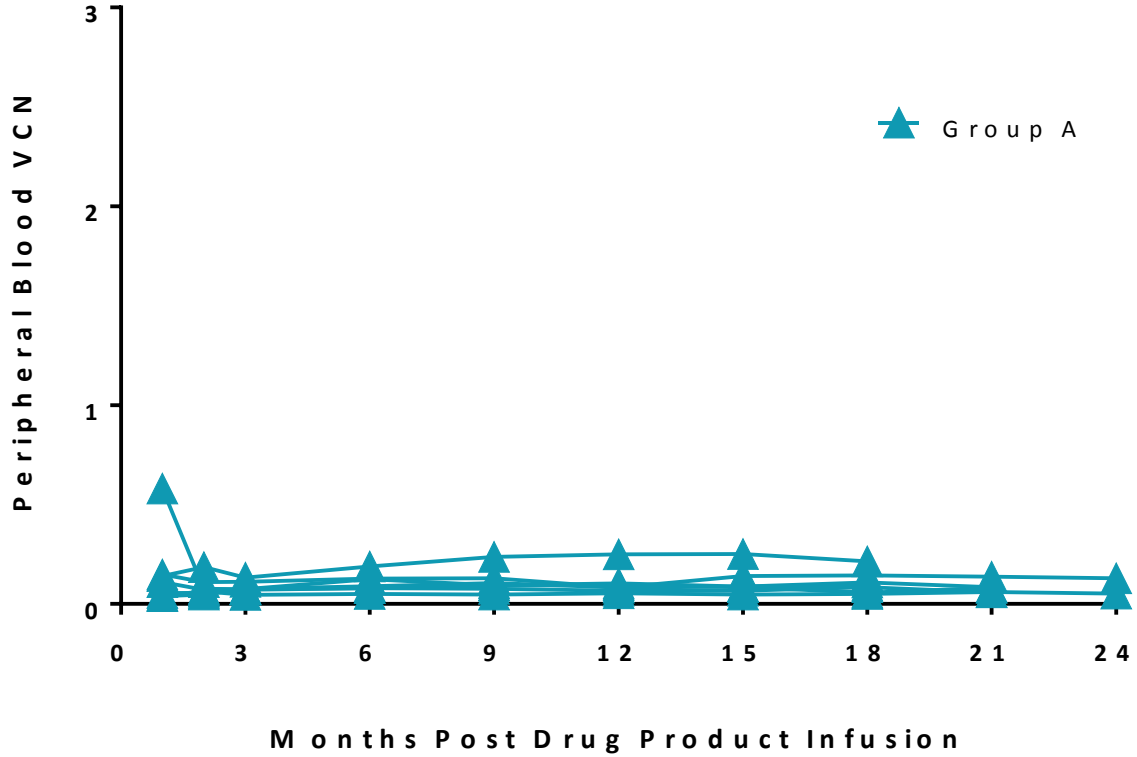
Data as of Oct 26, 2017; #Data as of Nov 30

DP VCN and peripheral blood VCN in Group A

VCN in drug product and peripheral blood



Peripheral blood VCN over time

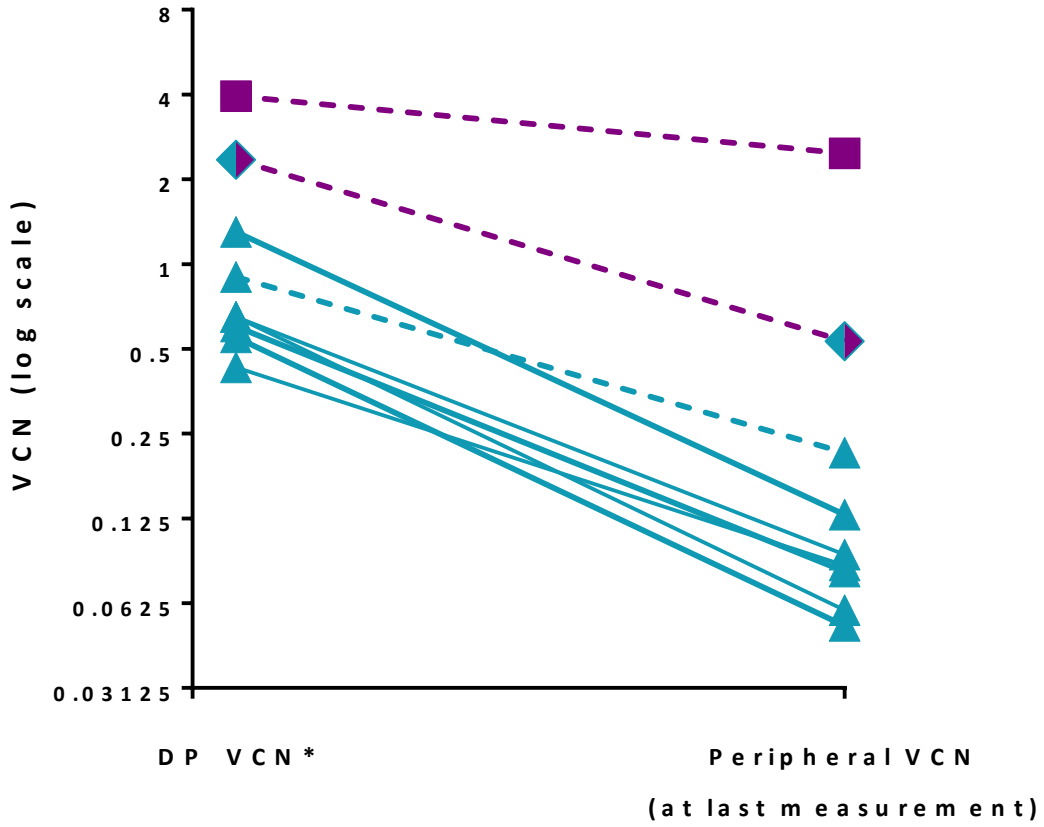


*Mean DP VCNs for patients with >1 DP lot; dashed lines for patients with pre-treatment transfusions

Data as of Oct 26, 2017

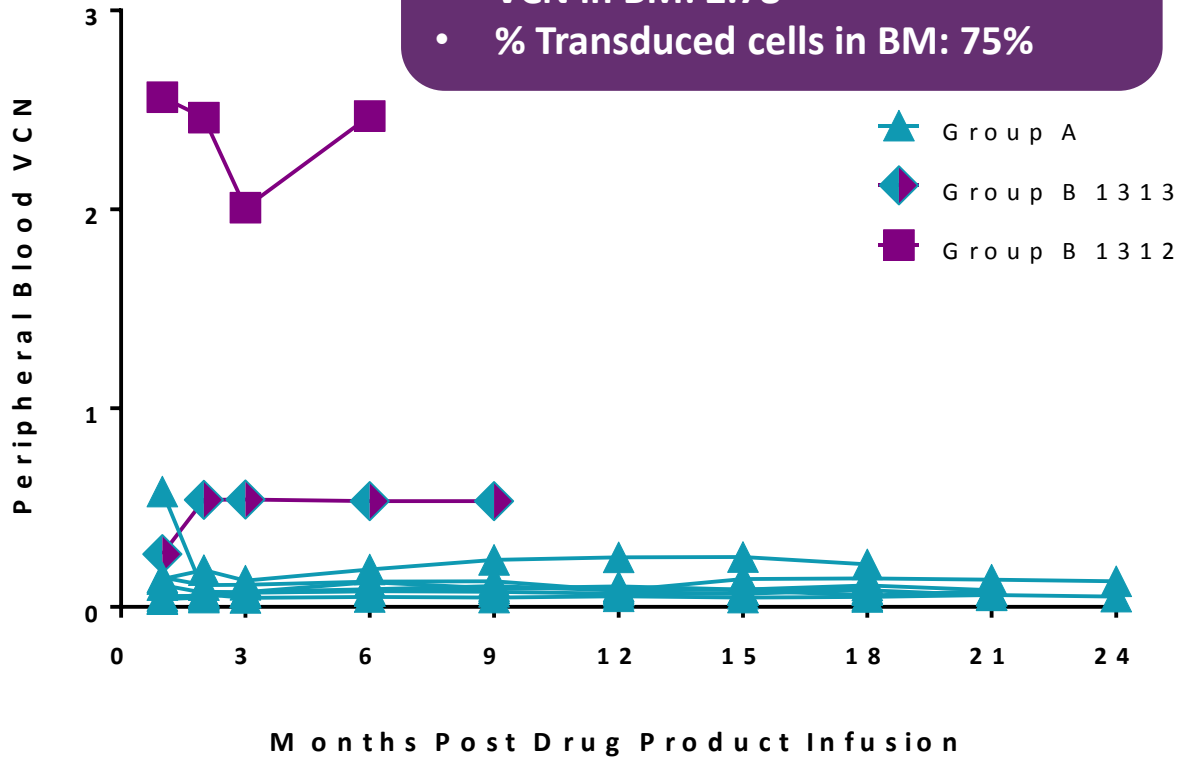
DP VCN and peripheral blood VCN are higher in patients in Group B

VCN in drug product and peripheral blood



Peripheral blood VCN over time

Pt. 1312: 6 month marrow analysis consistent with PB findings
- **VCN in BM: 2.78**
- **% Transduced cells in BM: 75%**

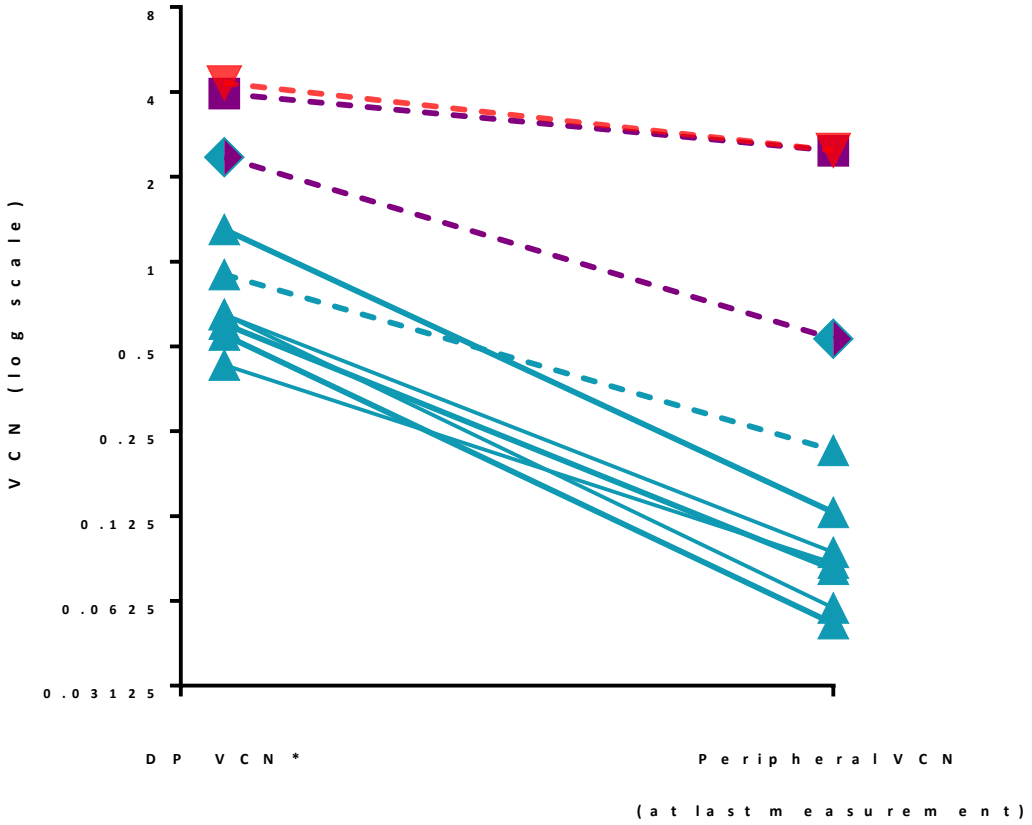


*Mean DP VCNs for patients with >1 DP lot; dashed lines for patients with pre-treatment transfusions

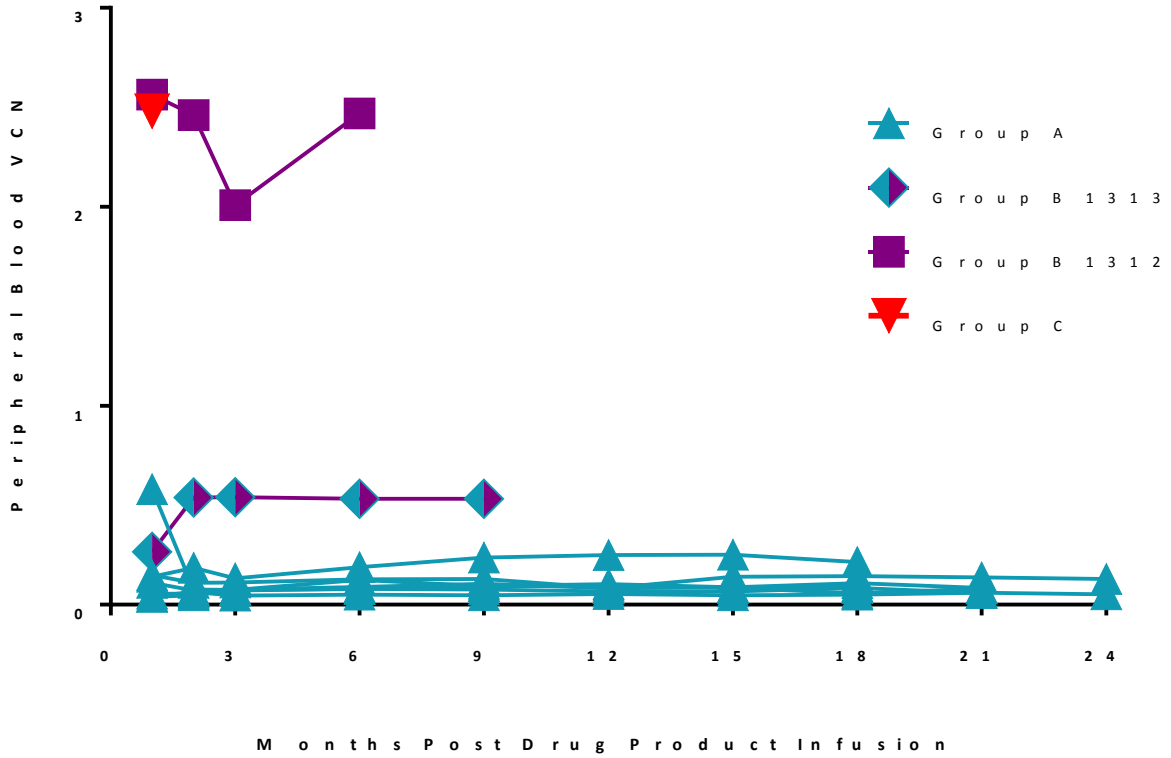
Data as of Oct 26, 2017 (GrpA), Nov 30, 2017 (Grp B)

DP VCN and peripheral blood VCN are higher in patients in Group B and C

VCN in drug product and peripheral blood



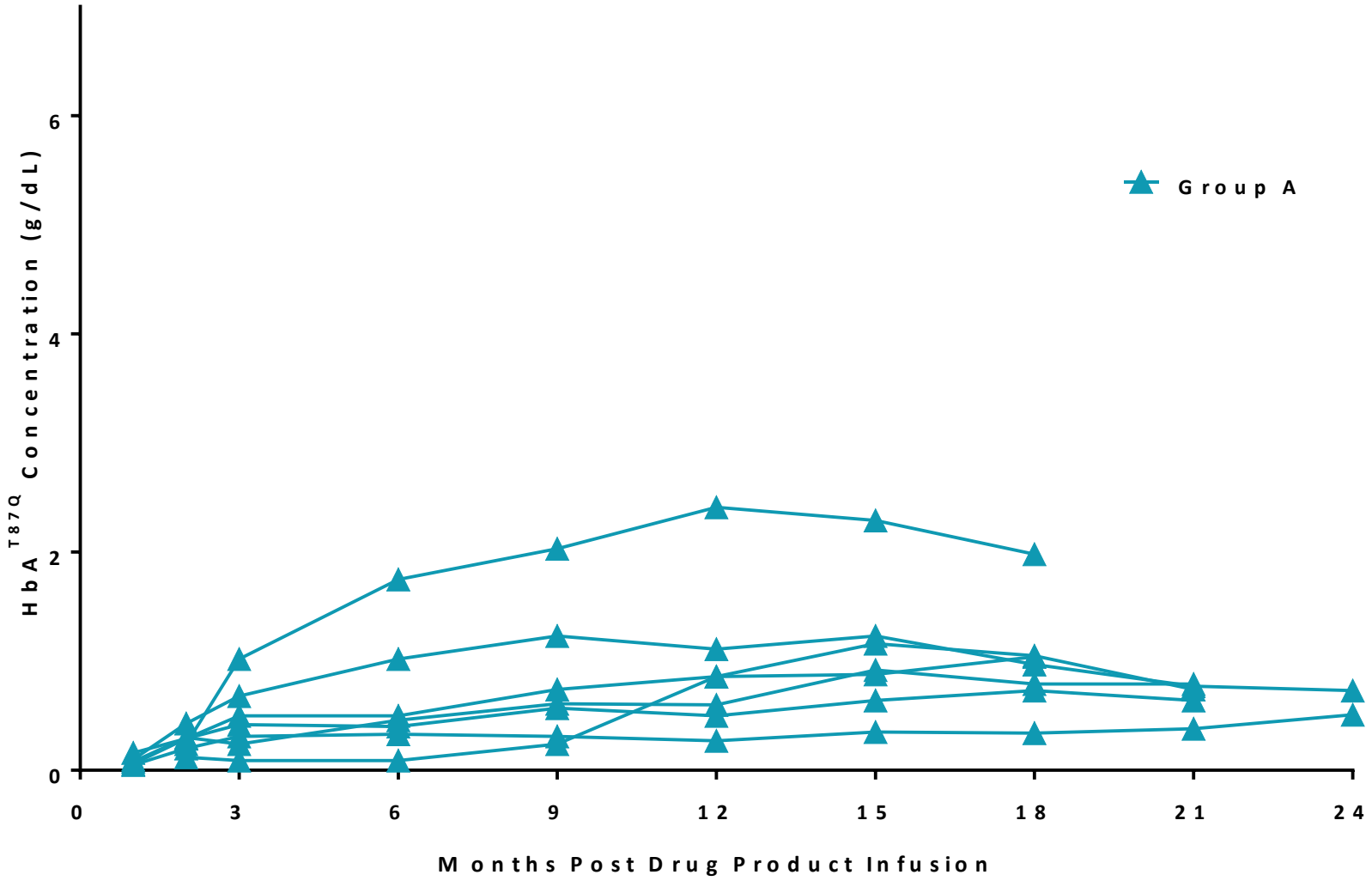
Peripheral blood VCN over time



*Mean DP VCNs for patients with >1 DP lot; dashed lines for patients with pre-treatment transfusions

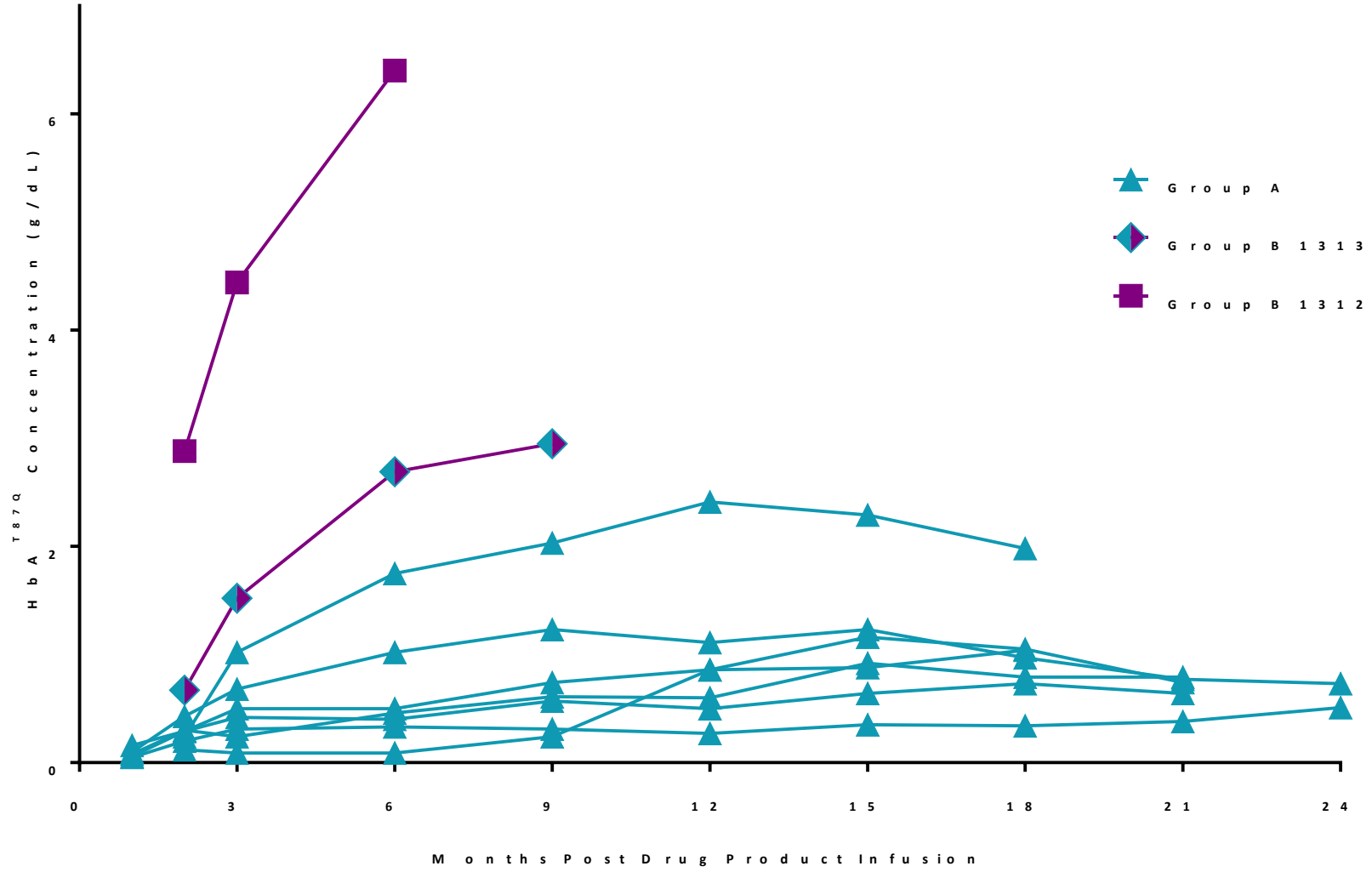
Data as of Oct 26 ’17(GrpA), Nov 30 ’17(Grp B), Dec 6 ’17(GrpC)

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



Data as of Oct 26, 2017 for Grp A

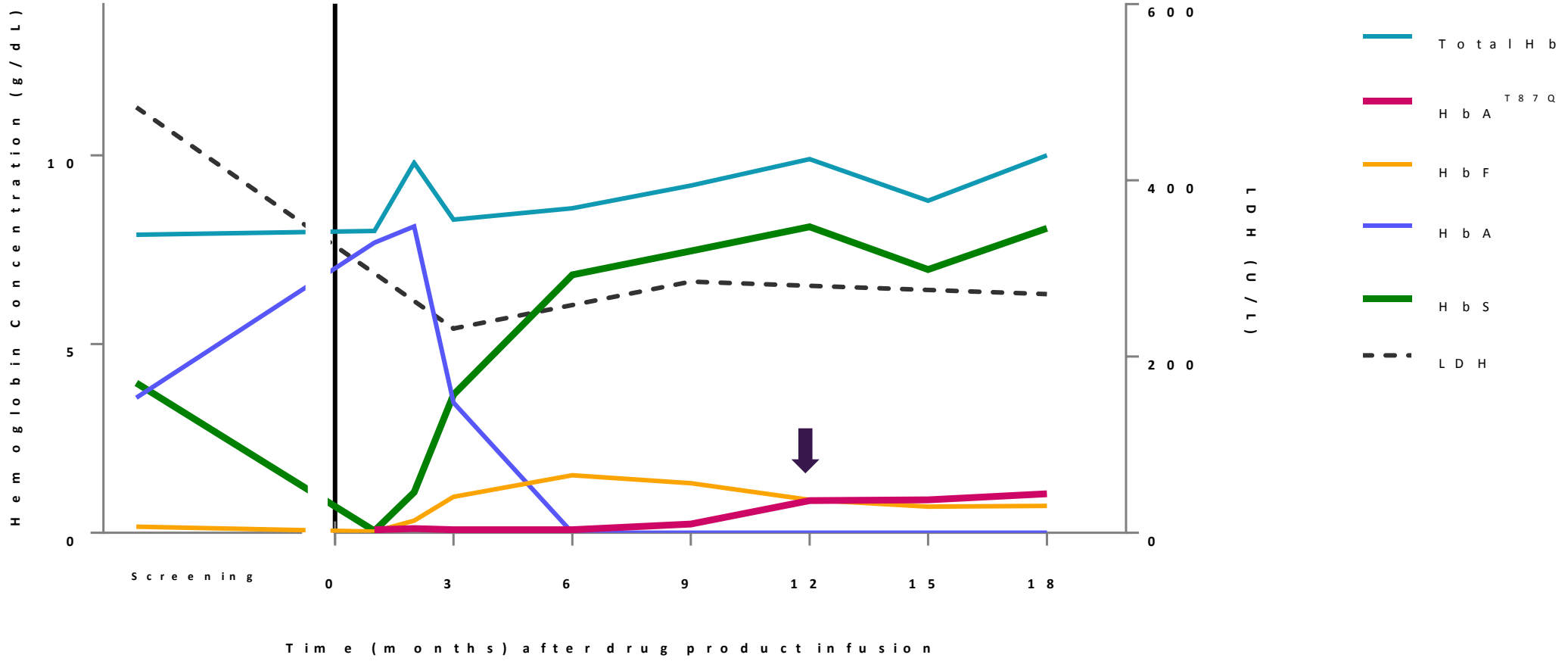
Patients in Group B demonstrate higher HbA^{T87Q} production



Data as of Oct 26, 2017 for Grp A; Nov 30 for Grp B Pt 1312

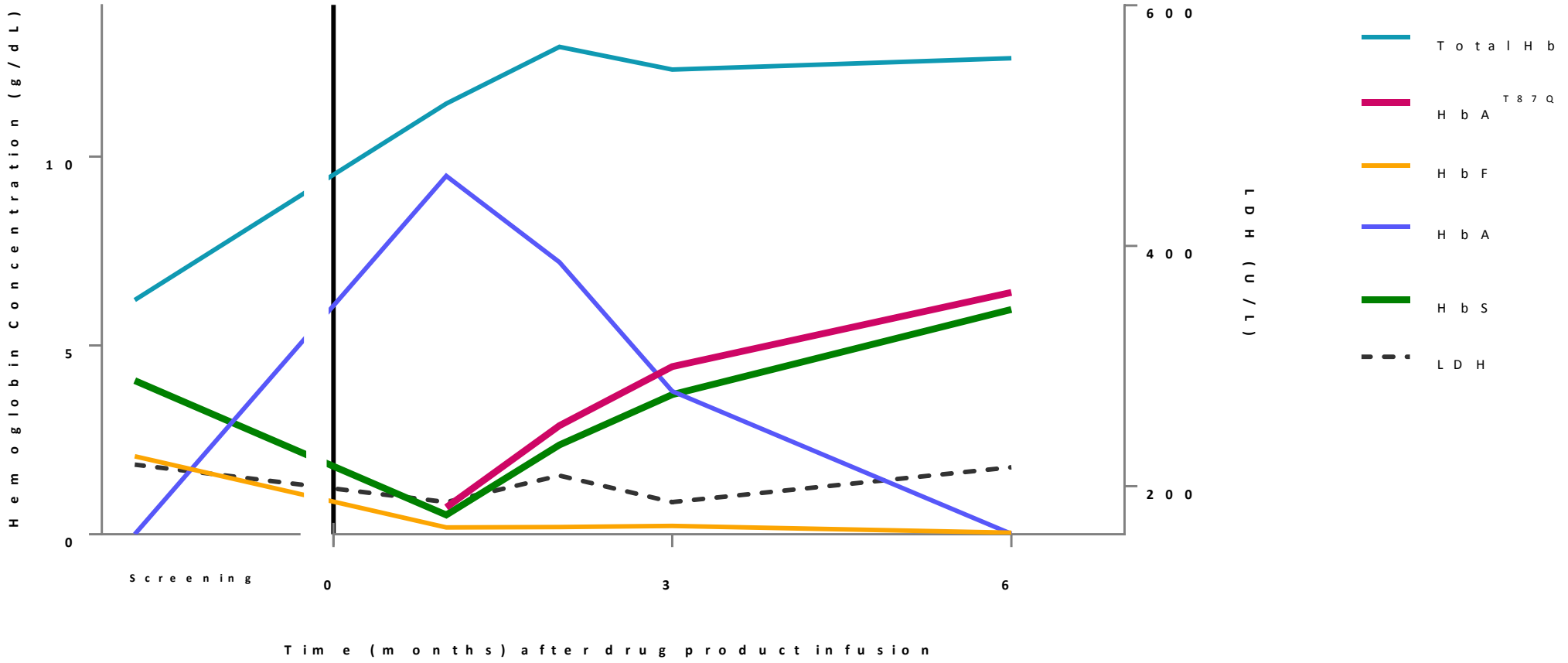
Biomarkers of hemolysis in Phase 1 HGB-206 Study: Patient 1310

Group A

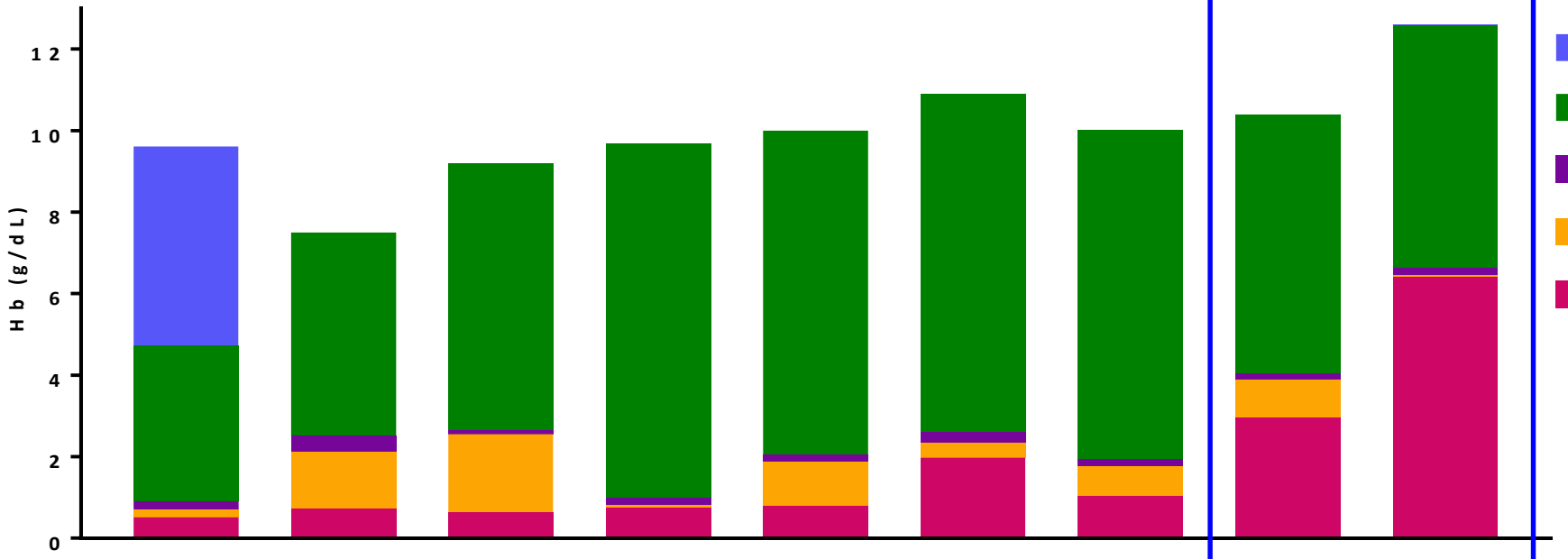


Biomarkers of hemolysis in Phase 1 HGB-206 Study: Patient 1312

Group B



Higher vector-derived Hb in patients treated under modified protocol and refined manufacturing process



Total Hb	9.6	7.5	9.2	9.7	10.0	10.9	10.0	10.4	12.6
	1301	1303	1304	1306	1308	1309	1310	1313	1312*
Follow up (m)	24	24	21	21	21	18	18	9	6
% HbA^{T87Q}	5	10	7	8	8	18	10	28	51
% HbF	2	18	21	1	11	3	7	9	0
% HbS	40	67	71	90	79	76	81	61	47

Data as of Oct 26, 2017; *Data as of Nov 30, 2017

Safety profile consistent with myeloablative conditioning

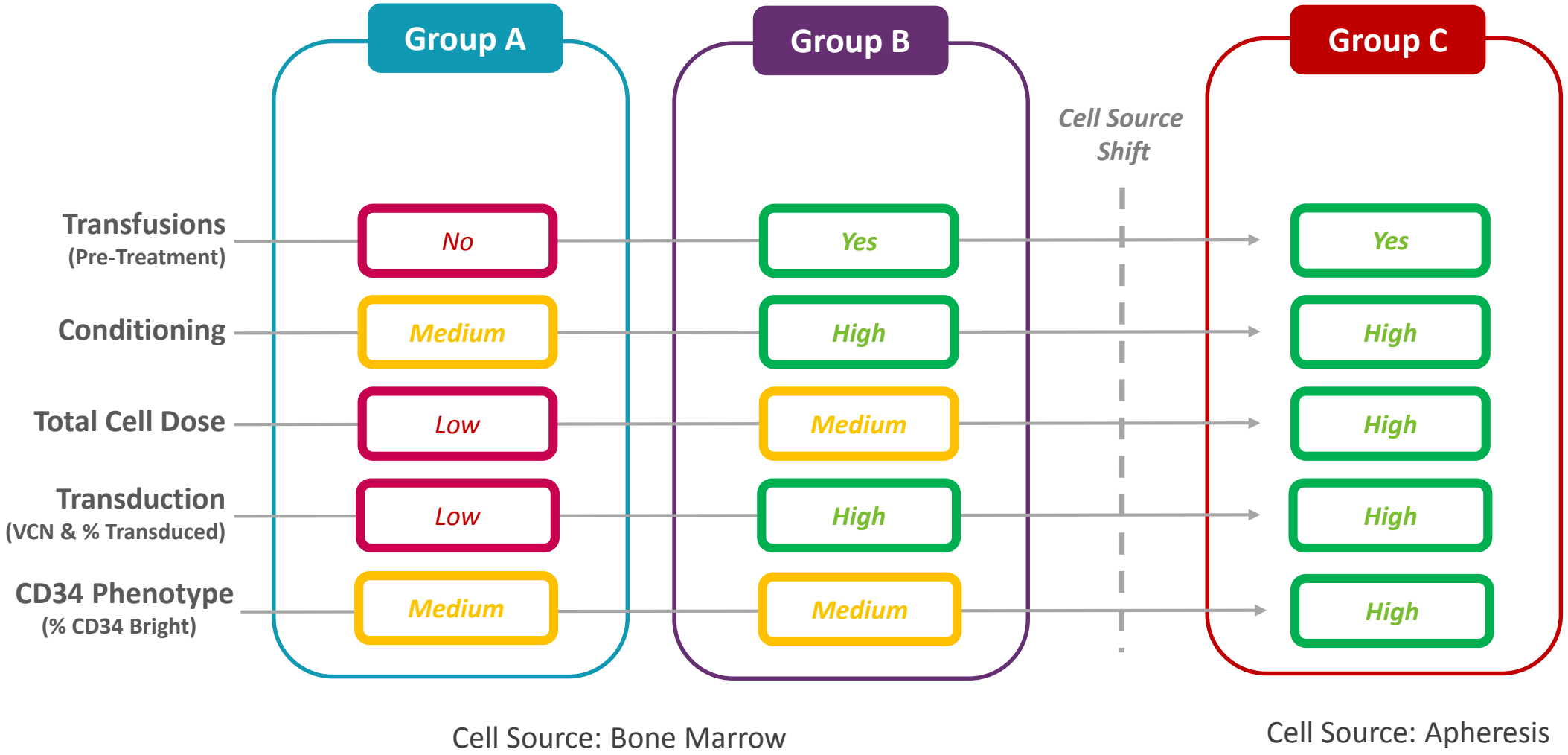
After LentiGlobin DP infusion

Non-hematologic grade ≥3 AEs post DP infusion reported in ≥2 patients	Incidence n[#] (%)
Sickle cell anemia with crisis	5 (55.6)
Febrile neutropenia	5 (55.6)
Stomatitis	7 (77.8)
Bacteremia	2 (22.2)
Pyrexia	2 (22.2)
Pharyngeal inflammation	3 (33.3)

[#]In 9 patients; 7 Group A and 2 Group B

- Grade ≥3 hematologic AEs post infusion consistent with myeloablative busulfan conditioning
- SAEs in 8 patients, most common being sickle cell anemia with crisis (n=4)
- 1 patient in Group C: no unexpected Grade ≥3 AEs, no SAEs or DP-related AEs*
- **1 AE (hot flush, Grade 1) considered related to LentiGlobin DP**
- **No replication competent lentivirus detected**
- **Continued highly polyclonal repopulation**

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



6 patients mobilized

DP manufactured for 4 patients

Tisdale J et al, ASH 2017 Abstract # 990

Summary: Phase 1 study of LentiGlobin gene therapy in patients with severe SCD

- Patients in Group A show that even modest amounts of vector-derived hemoglobin may provide clinical benefit via increased total hemoglobin
- Engraftment and safety profile consistent with previous findings
- Early data from patients in Group B (refined protocol and manufacturing) demonstrate:
  - Increased peripheral blood VCN
  - Vector-derived HbA^{T87Q} levels as high as 6.4 g/dL (51% of total Hb) at 6 months
- Plerixafor mobilization and apheresis to collect HSCs for DP manufacture may further improve drug product cell dose
- Future results from patients treated in Group C will determine the collective effects of all protocol and process changes

HGB-206 Study Sites and Investigators

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

- Alexis Thompson
- Katherine Hammond

Medical University of South Carolina, Charleston

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

Children's Hospital of Philadelphia, UPenn

- Janet Kwiatkowski
- Isaiah Somers

UCSF Benioff Children's Hospital, Oakland

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

Emory University, Atlanta

- Lakshmanan Krishnamurti
- Ashley Griffin

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

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

Columbia University Medical Center

- Markus Mapara
- Rachel Shields
- Monica Bhatia

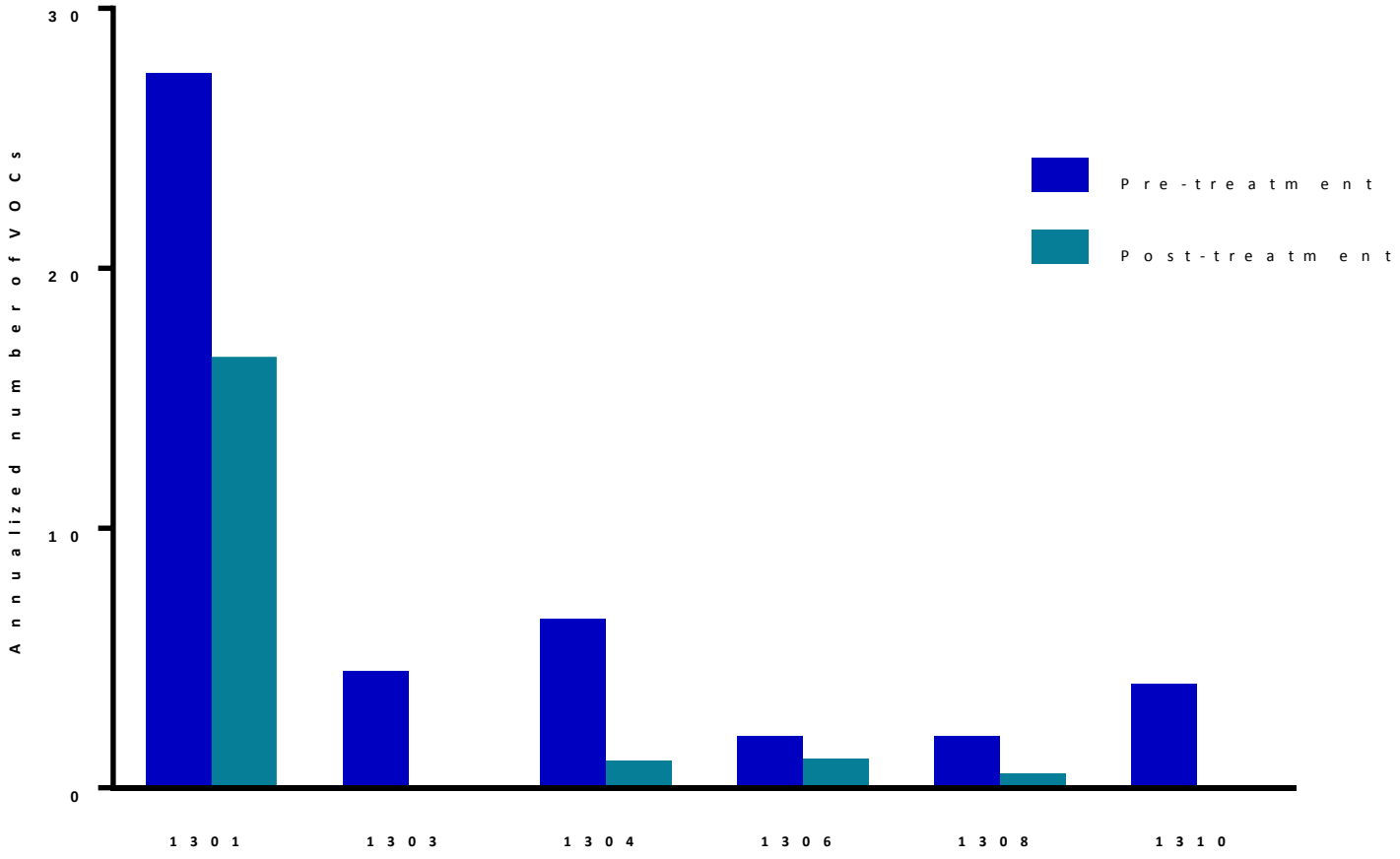
bluebird bio, Inc.

- Jean-Antoine Ribeil
- Mohammed Asmal
- Alexandra Miller
- Erin Whitney
- Kate Lewis
- Purvi Mody

Thank you to the study participants and their families

Back-up

Patients with >12 months follow-up have decreased rate of annualized aggregate VOCs after transplant



% decrease from baseline	39.6	100	83.8	44.5	71.3	100

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

Data as of Oct 26, 2017