ASH 2016 Abstract # 1176

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

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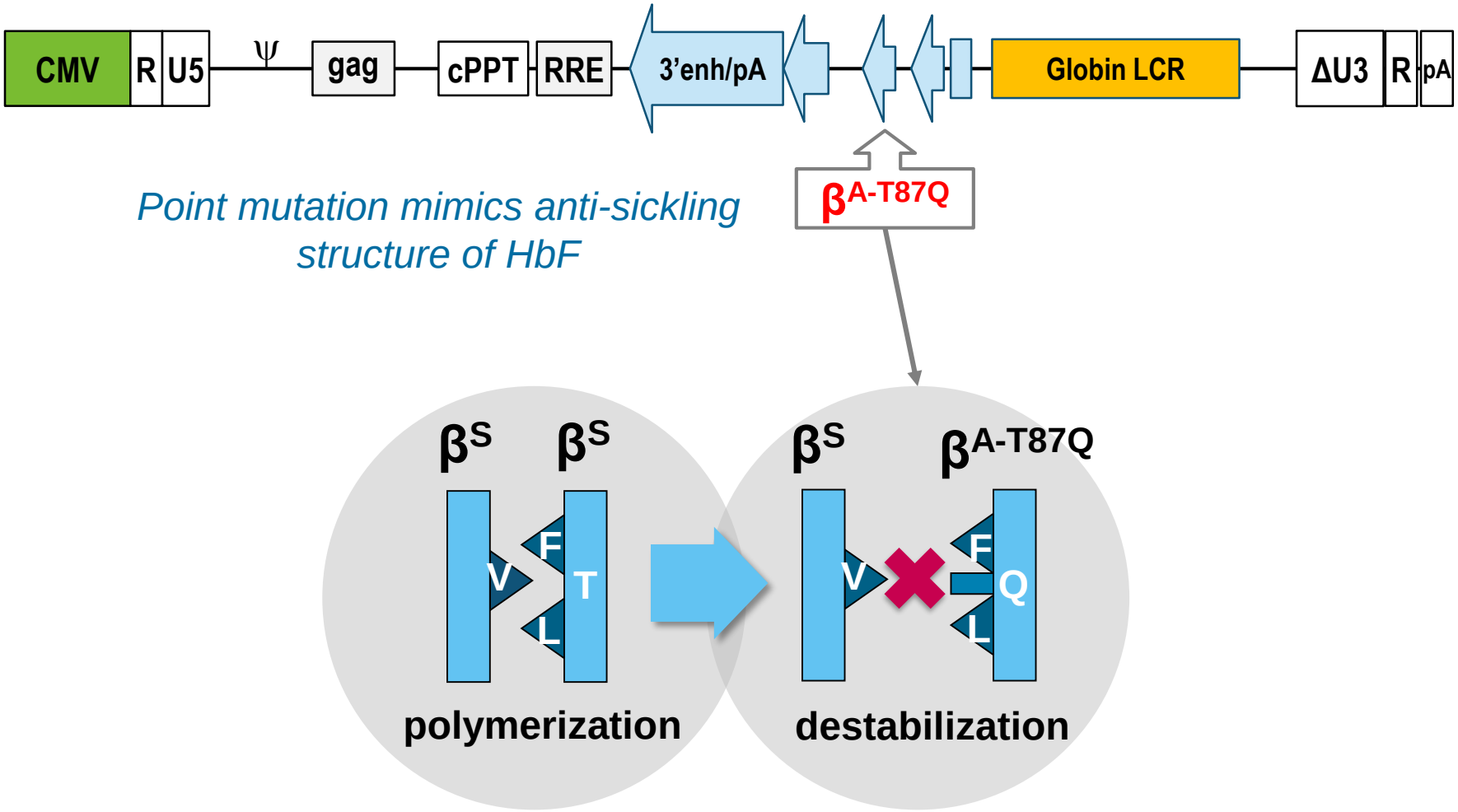
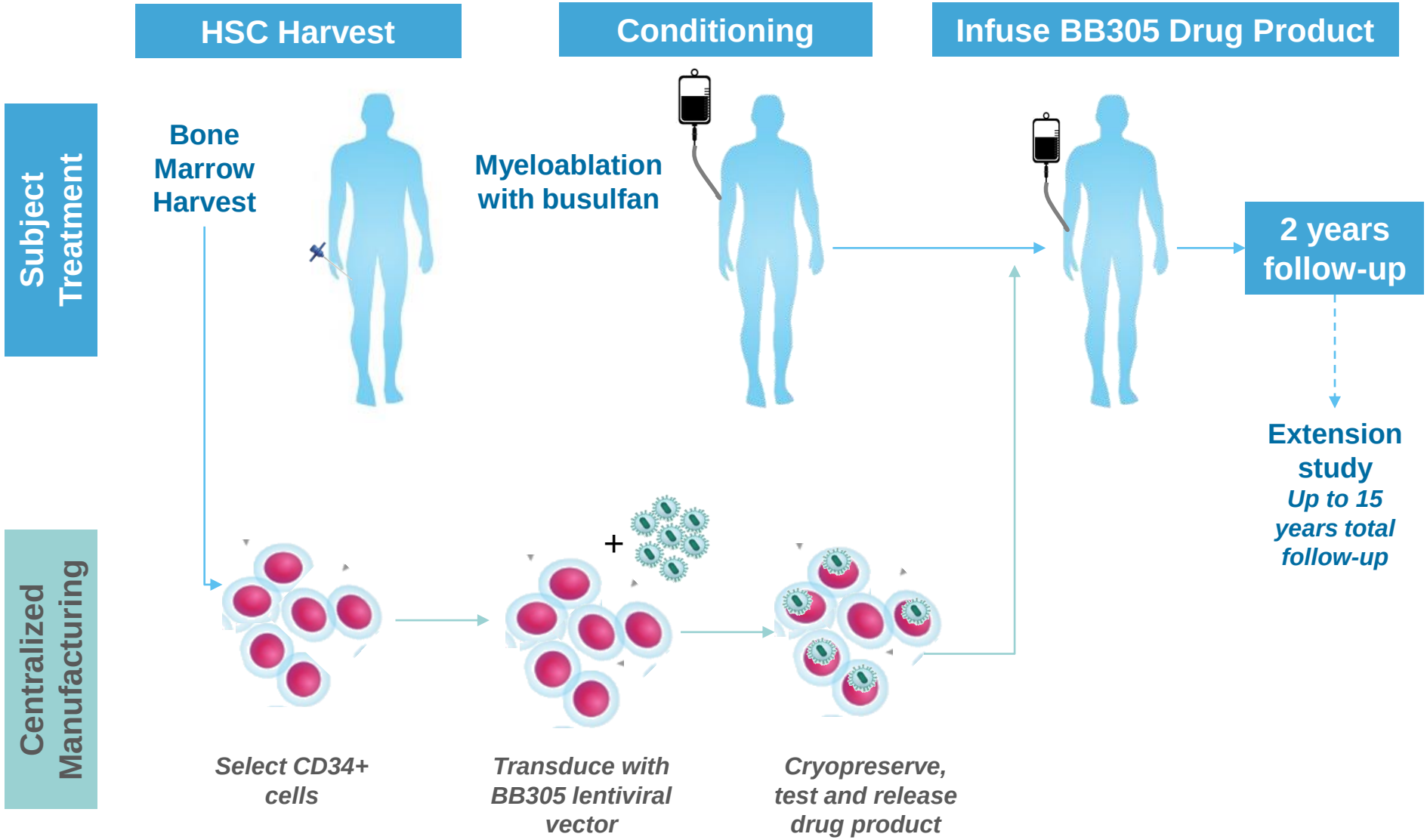
LentiGlobin BB305 lentiviral vector engineered to encode anti-sickling β^A-globin



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



Current status of HGB-206 study

Key enrollment criteria

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

Consented
N=13

*Ineligible N=2**

Bone marrow harvest planned or in progress N=2

Bone Marrow Harvest Complete
N=9

Manufacturing in progress N=1

Transduction Complete
N=8

Withdrew consent N=1

Drug Product Infused
N=7

Target: up to 29 treated subjects

*reasons for ineligibility: bilirubin levels (n=1), fertility concerns (n=1)

Patient and treatment characteristics

All treated patients (n=7) have a **history of severe sickle cell disease (SCD)** in 2 years prior to enrollment, despite hydroxyurea therapy

SCD History

Recurrent VOCs	*Stroke*	*Acute Chest Syndrome*	*Regular pRBC Transfusions*
6	1	6	1

Treatment Characteristics

Parameter	*Median (range)*
Age at enrollment (years)	26 (18 – 42)
Bone marrow harvests (n)	2 (1 – 4)
Target daily busulfan AUC (μM/min)	5000 (4400 – 5400)
LentiGlobin drug product cell dose ($x10^6$ CD34+ cells/kg)	2.1 (1.6 – 5.1)
LentiGlobin drug product vector copy number (VCN)	0.6 (0.3 – 1.3)

Results

Safety profile consistent with bone marrow harvest and myeloablative conditioning

Median follow-up: 11.5 months
range **8.1 – 17.1** months
N=7 treated patients

	Median (range)
Neutrophil engraftment (day)[1]	**22** (17 - 29)
Platelet engraftment (day)[2]	**56** (29 - 63)

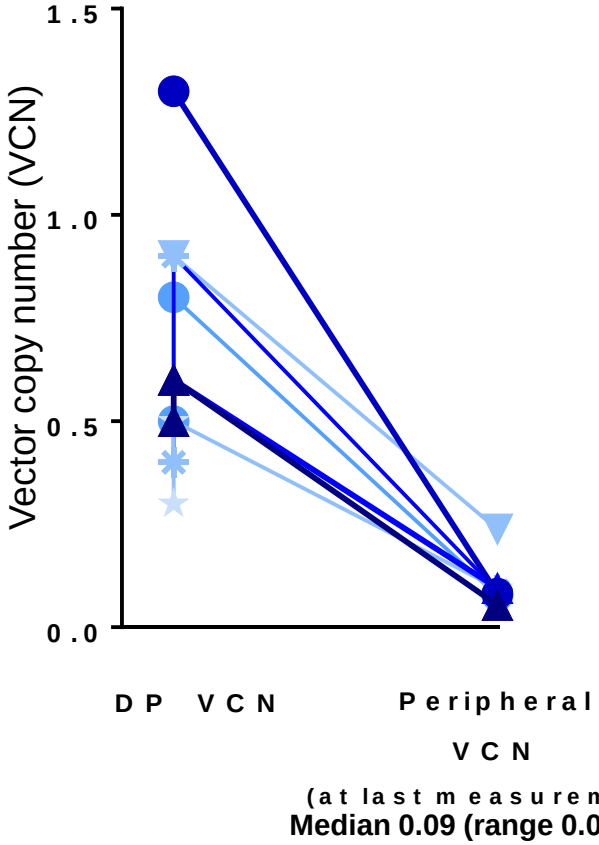
Most common non-laboratory Grade ≥3 AEs (occurring in ≥2 patients)	**# of patients (Day -8 to 43)[3]**
Febrile neutropenia	4
Stomatitis	5
Bacteremia	2
Sickle cell anemia with crisis	4
Fever	2
Pharyngeal inflammation	2

- 10 Grade 3 AEs related to bone marrow harvest were reported in 3 patients, including 1 SAE (pain/prolonged hospitalization)
- 6 patients experienced 1 or more SAE unrelated to LentiGlobin DP
- No AEs reported were related to LentiGlobin DP
- No replication competent lentivirus detected in any subject
- Highly polyclonal repopulation with no clonal dominance

1. Absolute neutrophil count ≥ 500; 2. Unsupported platelet count ≥ 50,000/µL. 3. No Grade ≥3 AEsAEs occurred in ≥2 patients after Day 43. Data as of November 9 2016.

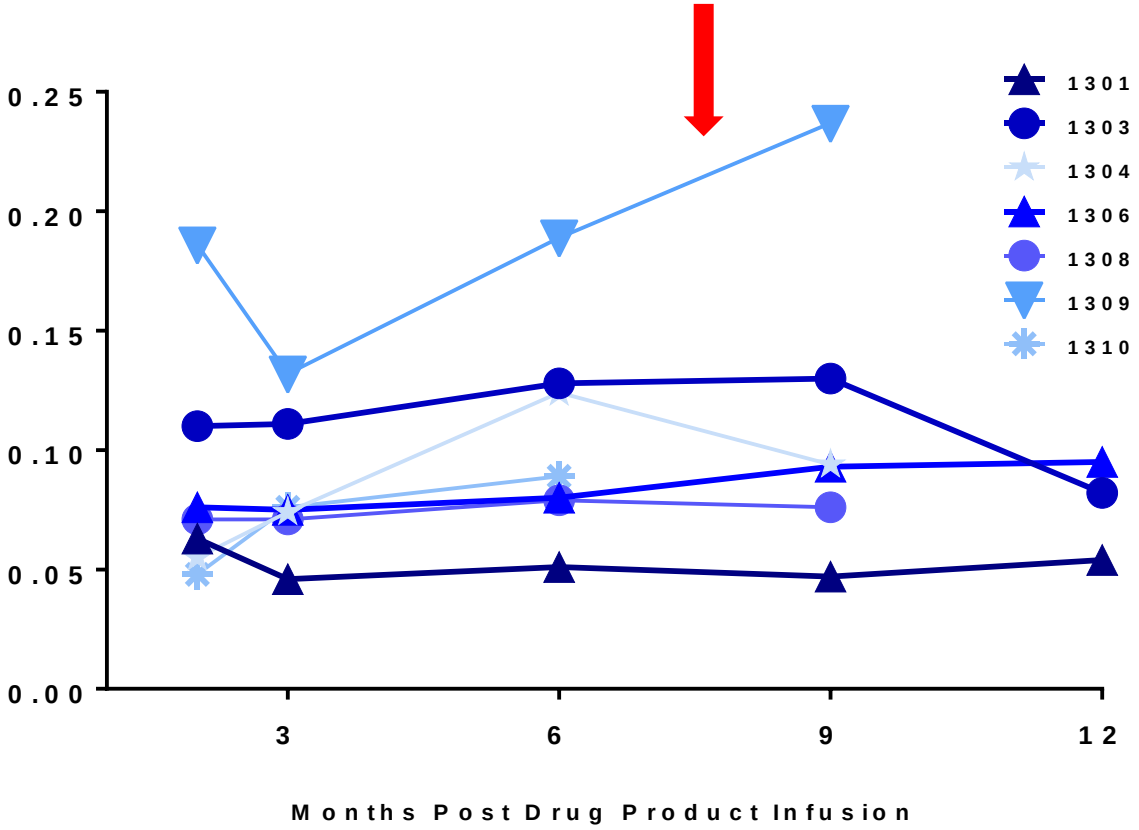
Decline in peripheral blood vector copy number (VCN) after drug product infusion

VCN drop from drug product to peripheral blood

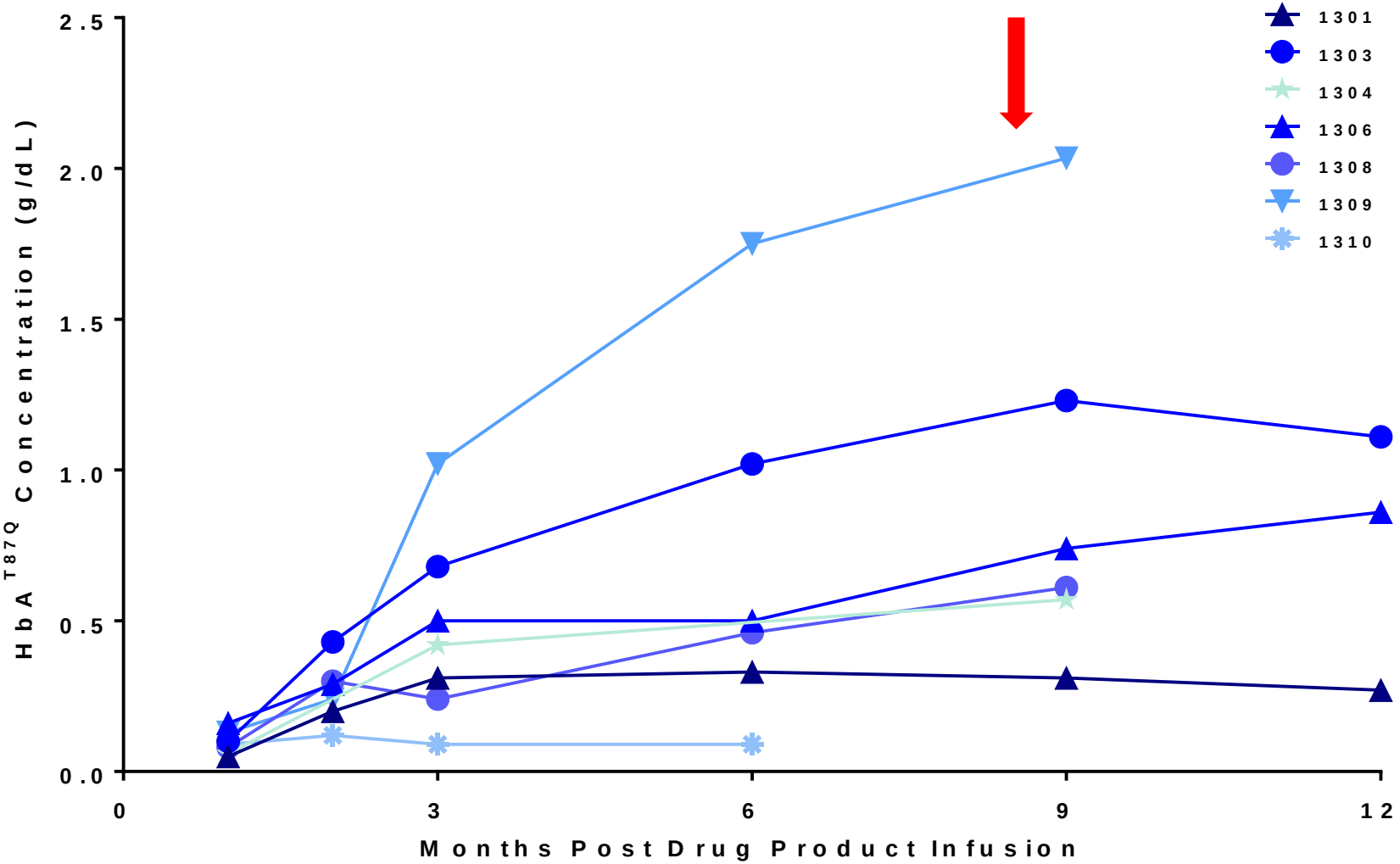


Median 0.09 (range 0.05 – 0.24)

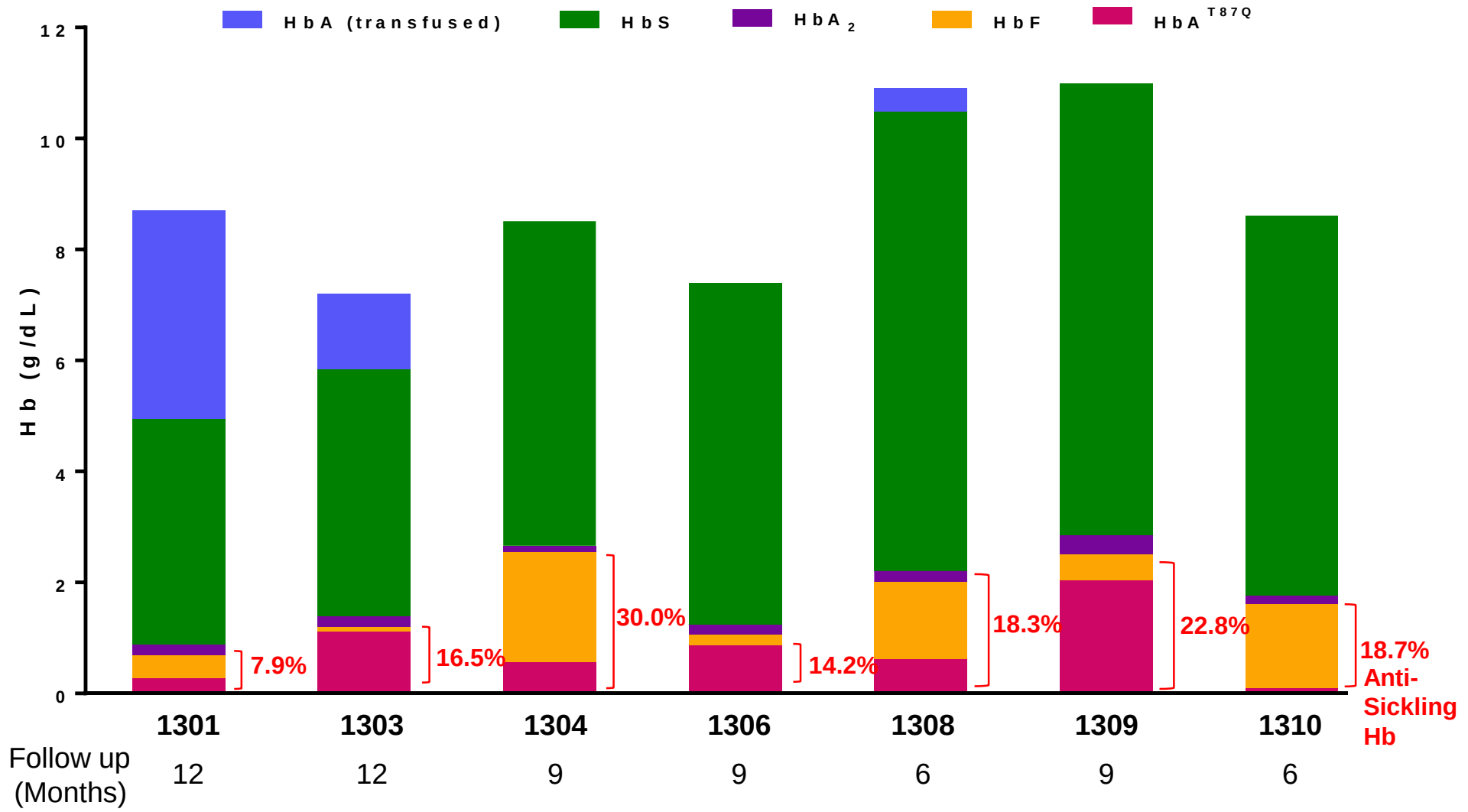
Peripheral blood VCN over time



All treated patients produce measureable HbA^{T87Q}



8% to 30% anti-sickling hemoglobin (HbA^{T87Q} + HbF) at last follow up

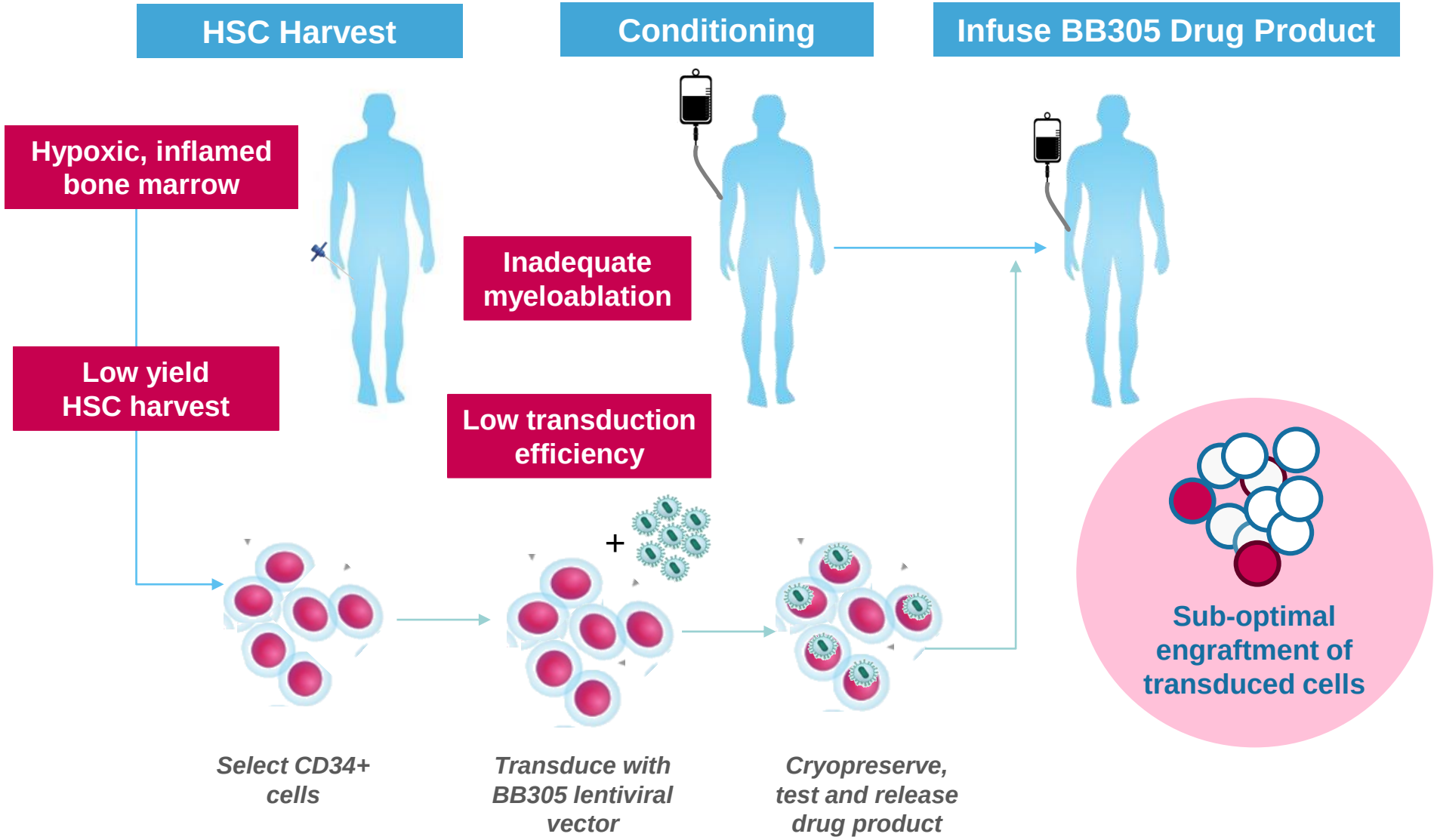


Interim Conclusions
&
Next Steps

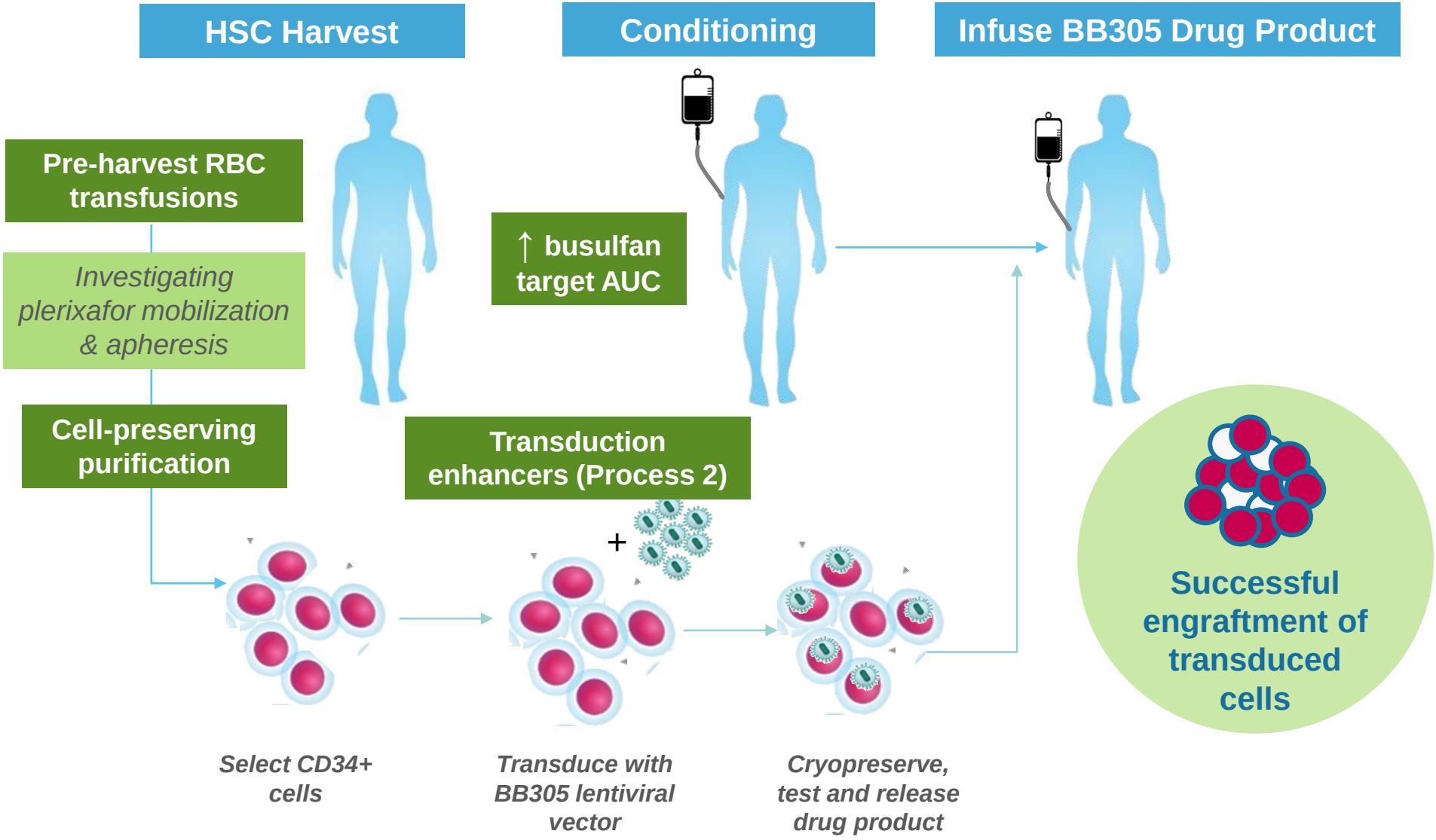
Interim summary – Where are we today?

- Study findings confirm feasibility of LentiGlobin autologous gene therapy for severe SCD
  - Successful bone marrow harvests and drug product manufacturing
  - Safety profile consistent with procedural requirements
  - No gene therapy-related AEs
  - HbA^{T87Q} production in all treated patients
- Challenges remain to achieve target level of anti-sickling hemoglobin in all patients
- Higher levels of anti-sickling hemoglobin are needed to optimize clinical benefit

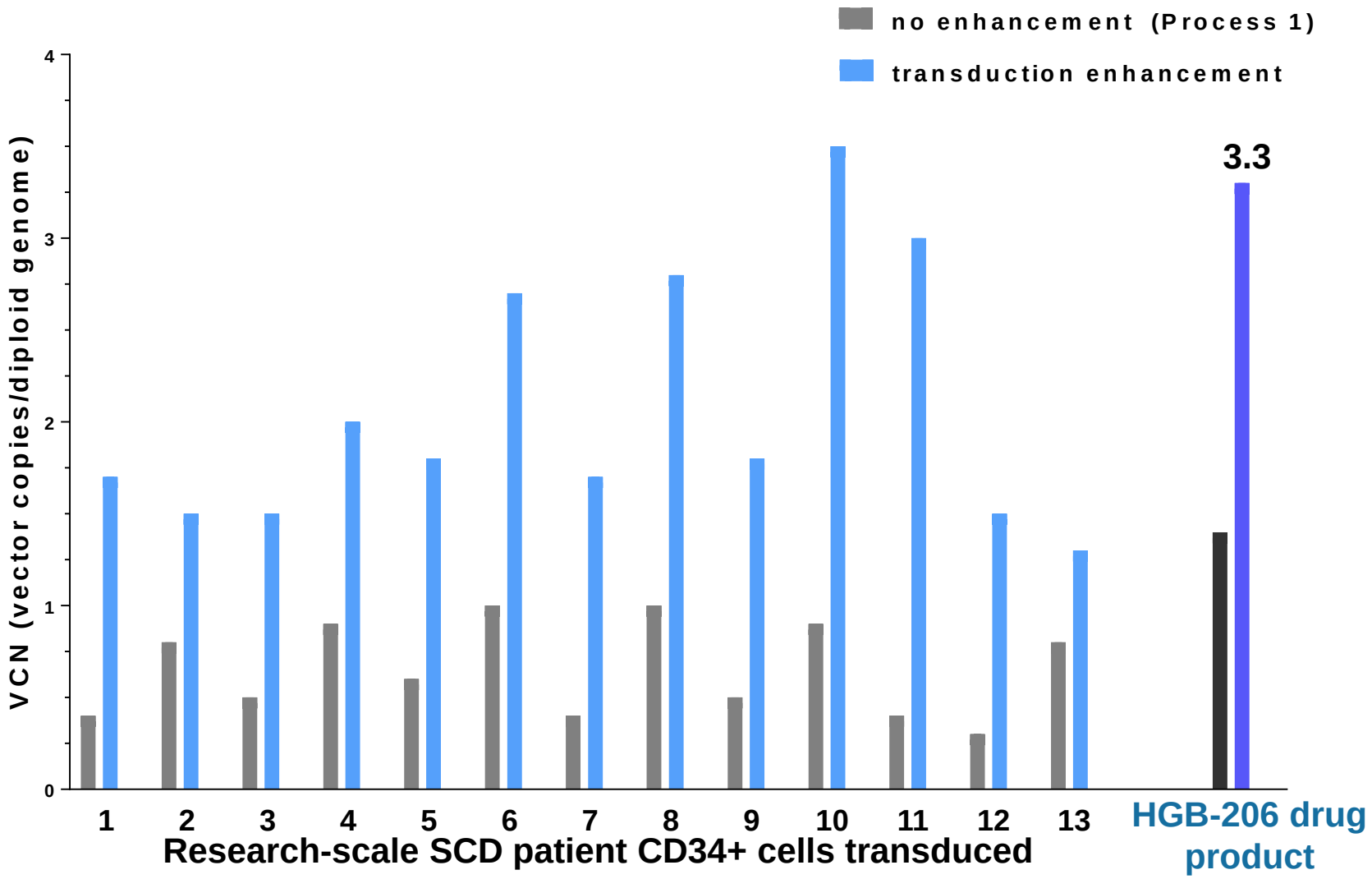
What we've learned: Challenges in SCD gene therapy



What we are doing: Multiple changes intended to improve engraftment and outcomes



LentiGlobin manufacturing with transduction enhancers increases DP VCN in SCD CD34+ cells



Data as of November 30, 2016

Key Takeaways

- Established feasibility of autologous transplant with genetically modified stem cells for sickle cell disease
- Treatment leads to measurable HbA^{T87Q} production in all treated patients, approaching target levels in some patients
- Changes to manufacturing and treatment protocol have been introduced with the goal of increasing HbA^{T87Q} production

HGB-206 Study Sites and Investigators

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- Kate Lewis
- Yvonna Fisher-Jeffes

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