For video

Resolution of Serious Vaso-Occlusive Pain Crises and Reduction in Patient-Reported Pain Intensity: Results from the Ongoing Phase 1/2 HGB-206 Group C Study of LentiGlobin for Sickle Cell Disease (bb1111) Gene Therapy

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DISCLOSURES

Janet L. Kwiatkowski

- Advisory boards with Agios, Celgene (Bristol Myers Squibb), Silence Therapeutics
- Honoria from bluebird bio

Sickle cell disease is characterized by high morbidity and early mortality

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- Sickled, rigid RBCs caused by HbS polymerization are prone to hemolysis, resulting in chronic hemolytic anemia, vasculopathy, and VOEs that lead to high morbidity and early mortality[1–3]
- >50% mortality before 45 years of age (β^S/β^S)[2]
- Curative therapies are needed
  - <15% of patients with SCD have an HLA-matched sibling donor[4,5]
- Gene therapy offers an alternative option to allogeneic HSCT

1. Kato GJ, et al. Nat Rev Dis Primer. 2018;4:18010; 2. Hassell K., Am J Prev Med 2010; 3. Kanter, et al. Blood Rev. 2013;27(6):279- 287; 4. Mentzer WC et al. Am J Pediatr Hematol Oncol. 1994; 16:27-29; 5. Walters MC et al. Biol Blood Marrow Transplant. 2001;7:665-673 RBC, red blood cell; Hbs, sickle hemoglobin; SCD, sickle cell disease; VOE, vaso-occlusive event.

HGB-206: An open-label, multicenter, phase 1/2 study of LentiGlobin gene therapy (bb1111) in patients with severe SCD

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Group C Enrollment Criteria

- ≥ 12 and ≤ 50 years of age
- $\beta^S\beta^S$, $\beta^S\beta^0$, $\beta^S\beta^+$ genotype
- History of severe VOEs*
- Hydroxyurea failure or intolerance

Enrollment Completed
(NCT02140554)

Group C Key Outcomes

- Complete resolution of severe VOEs
- Weighted average HbA^{T87Q} ≥ 30% of unsupported total Hb for ≥ 6 months post-DP
- Weighted average: unsupported total Hb increase ≥ 3 g/dL vs baseline or total Hb ≥ 10 g/dL for ≥ 6 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, acute hepatic sequestration, and acute splenic sequestration. Additionally, priapism events that require visit to medical care facility (without inpatient admission) are sufficient to meet severe VOE criterion.

DP, drug product; ER, emergency room; Hb, hemoglobin; IV, intravenous; SCD, sickle cell disease; VOE, vaso-occlusive event.

HGB-206: Study Design

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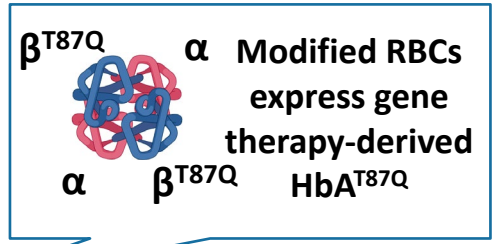
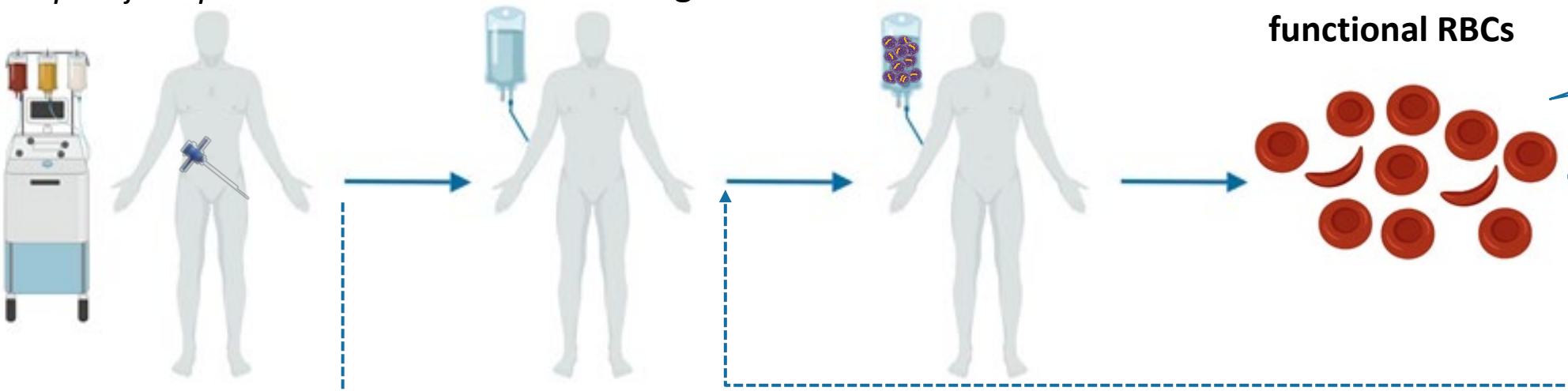
HSC collection
Bone marrow harvest or mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs



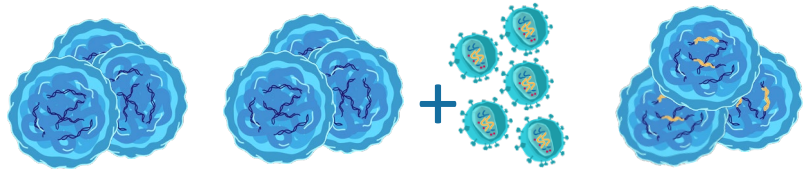


2-yr follow-up

Long-Term Follow-Up Study (NCT04628585)

	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 centralized manufacturing



Select CD34+ cells

Transduce with BB305 lentiviral vector

Cryopreserve, test, release DP

DP, drug product; HSC, hematopoietic stem cell, PB, peripheral blood; RBC, red blood cell.

HGB-206 Group C: Study disposition

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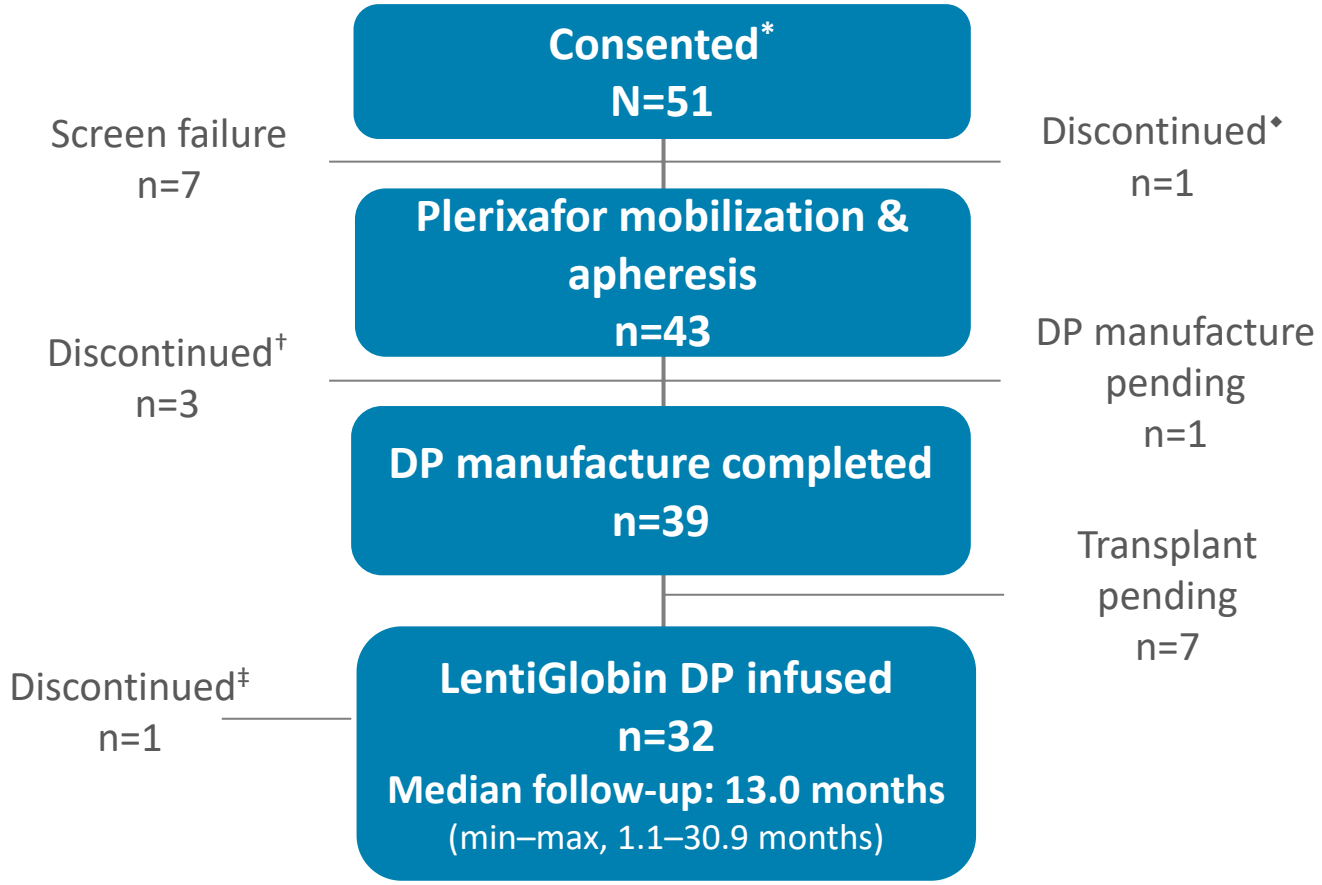

*Currently active, not recruiting; ◆1 withdrew consent; †1 withdrew consent, 1 withdrew at investigator discretion, 1 mobilization failure; ‡1 death.

DP, drug product; max, maximum; min, minimum.

HGB-206 Group C: Patient characteristics for ITT population

N=43 Patients who started cell collection

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Parameter	N=43
Age at consent, years, median (min–max)	**24** (12–38)
Age category 18–50 years, n 12– < 18 years, n	 **34** **9**
Gender, n	**18F 25M**
Genotype, n	**40** β^S/β^S **2** β^S/β^0 **1** β^S/β^+
SCD history	
Severe VOEs*, n Annualized no. of events, median (min–max)	**39** **3.5** (0.5–16.0)
ACS, n Annualized no. of events, median (min–max)	**10** **0.5** (0.5–1)
Priapism, n	**2**
Any history of stroke, n	**6**

A severe VOE is as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or emergency room observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration

ACS, acute chest syndrome; F, female; ITT, intent to treat; M, male; max, maximum; min, minimum; no., number; SCD, sickle cell disease; sVOE, severe vaso-occlusive event.

HGB-206 Group C: Treatment and drug product characteristics

N=32 Infused Patients

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Parameter	N=32 Median (min–max)
Treatment characteristics	
No. of mobilization cycles	**2** (1–4)
CD34+ cells collected per mobilization cycle, x10^6 cells/kg	**10.4** (3.9–55.4)
Estimated average busulfan AUC, min*µmol[†]	**4843** (1445[⬥]–7322)
Neutrophil engraftment, ANC ≥ 500 /µl x 3 days, days	**19.5** (12–35)
Platelet engraftment, platelets > 50k /µl x 3 days, days[‡]	**30** (18–136)
Duration of hospitalization[§], days	**35** (26–65)
Drug product characteristics (per patient)	
Vector copy number, copies/diploid genome	**3.8** (2.3–5.7)
CD34+ cells transduced, %	**80.2** (63–93)
CD34+ cell dose, x10^6 cells/kg	**6.8** (3.0–24.0)

[†]5 patients pending AUC result; [⬥] Data error is being corrected; [‡]3 patients pending platelet engraftment at days 29, 30, and 39 post-DP infusion, but on their way to achieving engraftment; [§] Duration of hospitalization from conditioning to discharge.

ANC, absolute neutrophil count; AUC, area under the curve; DP, drug product; max, maximum; min, minimum; no., number.

HGB-206 Group C: Complete resolution of VOEs ≥ 6 months post-LentiGlobin treatment

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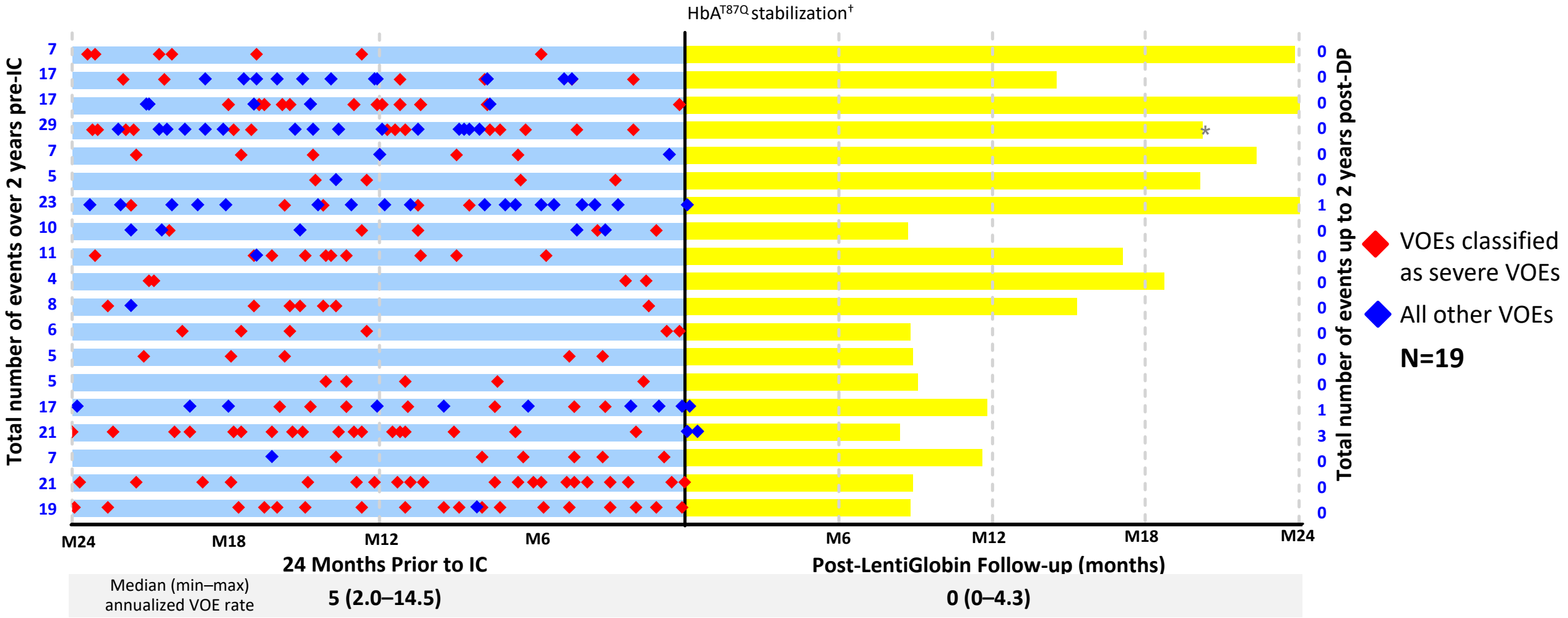

Protocol VOEs are shown; Patients with ≥ 4 sVOEs at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included. A VOE includes episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than 2 hours and severe enough to require care at a medical facility, a VOE includes acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration; †HbA^{T87Q} expression stabilizes within 6 months; *One death, unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.
Note: In the last datacut, one patient had a non-serious VOC at Day 107. The event is recorded as an investigator reported VOE but does not meet the definition of a protocol VOE.

DP, drug product; IC, informed consent; max, maximum; min, minimum; sVOEs, severe VOEs; VOC, vaso-occlusive crisis; VOE, vaso-occlusive event.

HGB-206 Group C: Decrease in patient-reported pain intensity

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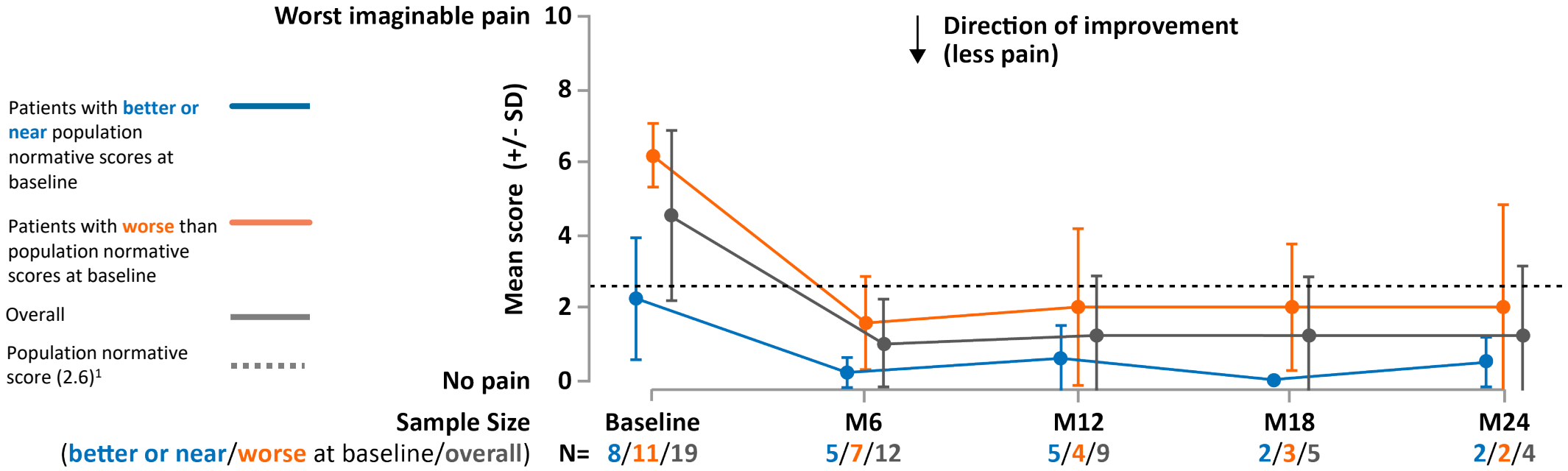
PROMIS-57 Pain Intensity NRS



Patients with baseline values (n):	Baseline though M24
Better or near population normative values	Improvement noted at M6 and were generally sustained through M24
Worse than population normative values	Improvement in pain to levels better than population norm values were observed at M6 and were sustained through M24
Overall	Improvement in pain intensity was observed irrespective of baseline values relative to population norm

Average pain (0–10) over the past 7 days; Mean score, SD I depicted 1. PROMIS Cooperative Group. 2020. PROMIS Reference Populations. Available at https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/reference-populations. Accessed Nov, 2020

NRS, Numeric Rating Scale; PROMIS, Patient Reported Outcomes Measurement Information System; SD, standard deviation

HGB-206 Group C: Median HbA^{T87Q} ≥ 40% at ≥ 6 months post-LentiGlobin treatment

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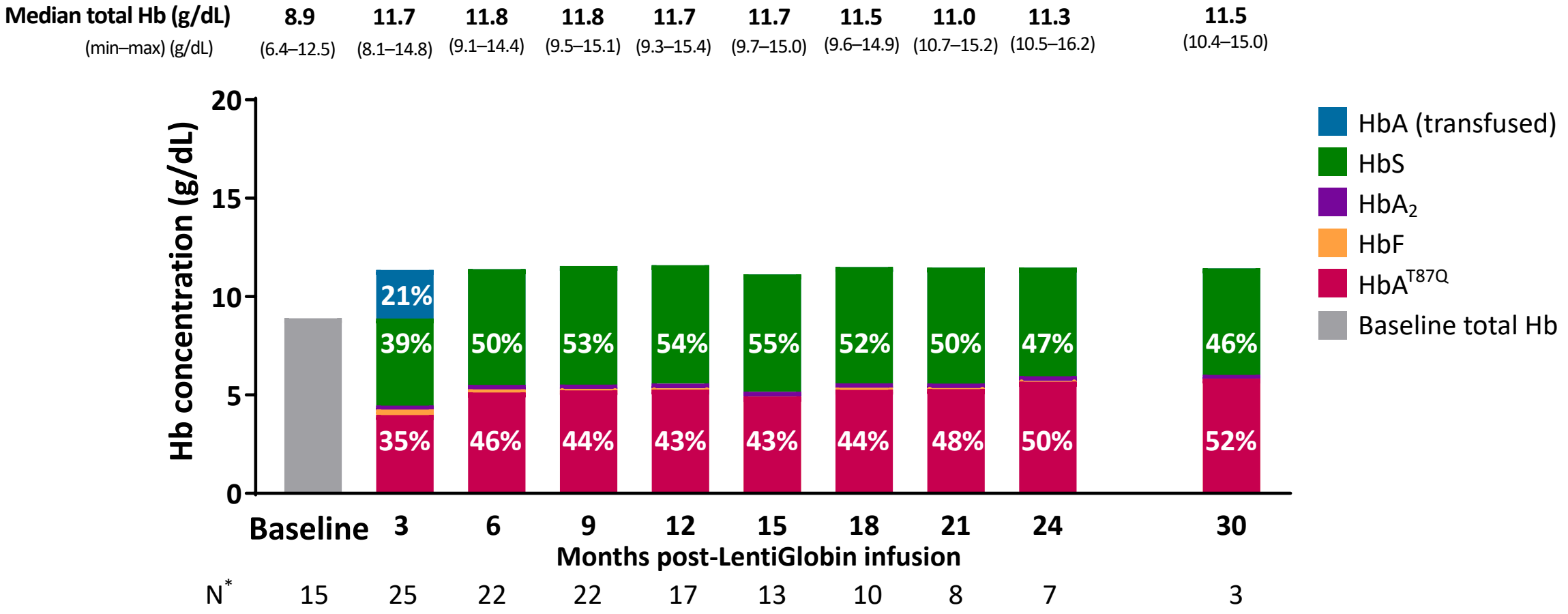

- **HbA^{T87Q} expression was near-pancellular** ≥ 6 months post-LentiGlobin treatment
  - Single RBC western assay was performed in a subset of HGB-206 Group C patient samples and the average Proportion of RBCs Containing $\beta^{A\text{-}T87Q}$ from LentiGlobin treated patient is ~90% by Month 18

% represents median Hb fraction as % of total Hb; *Number of patients with data available. Hb, hemoglobin; max, maximum; min, minimum.

HGB-206 Group C: Hemolysis and erythropoiesis markers approaching near-normal levels post-LentiGlobin treatment

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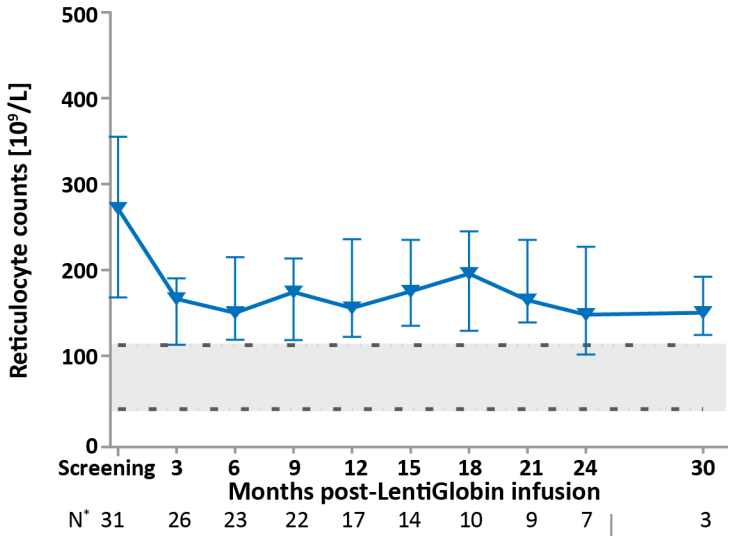
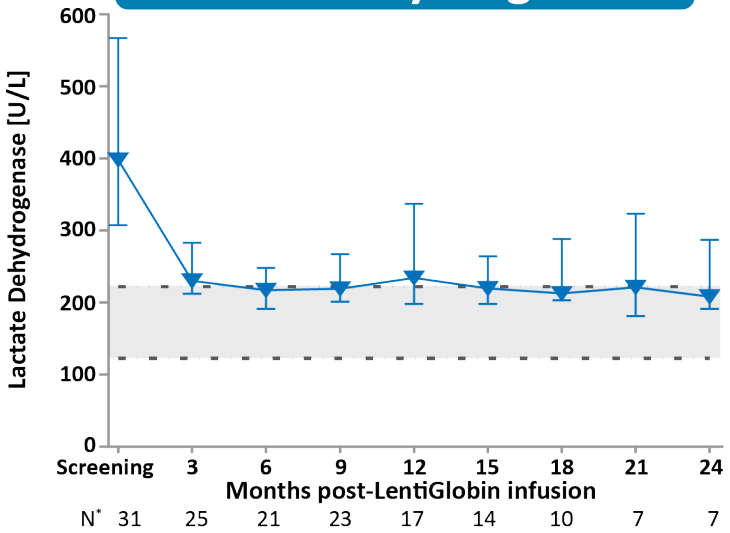
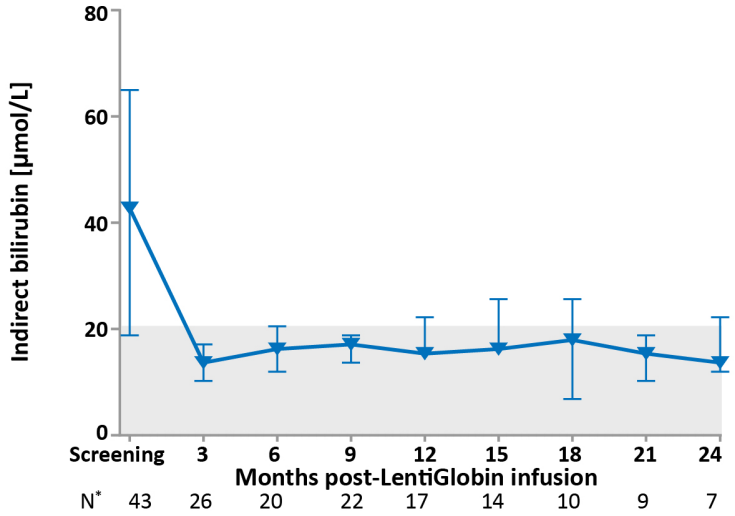
Reticulocyte counts

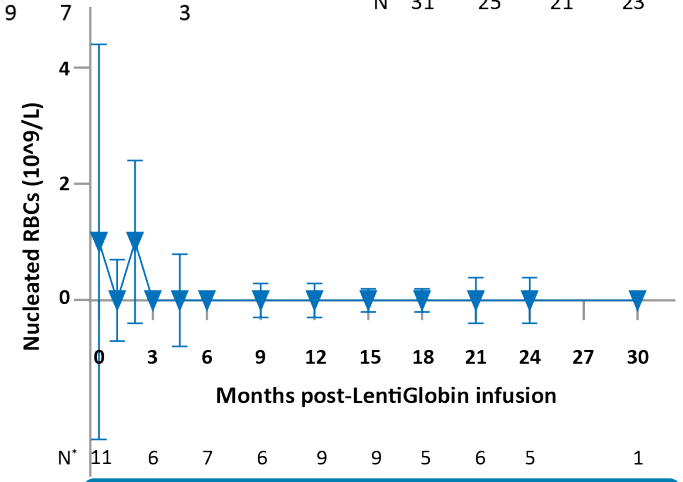


Lactate dehydrogenase

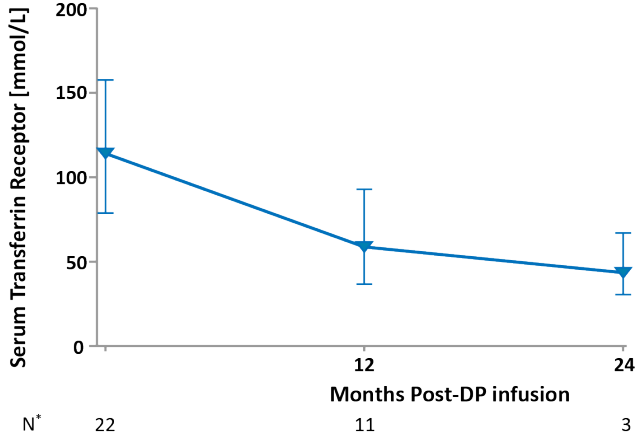


Indirect bilirubin





Nucleated RBCs



Serum transferrin receptor

Median (Q1, Q3) depicted; Dot-dash lines denote lower and upper limits of normal values; *Number of patients with data available. DP, drug product; Q1, quartile 1; Q3, quartile 3; RBC, red blood cell.

HGB-206 Group C: Safety profile post-LentiGlobin treatment

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Treatment-emergent ≥ Grade 3 AEs *Reported in ≥ 2 patients*[*]	**N=32** n (%)
Stomatitis	21 (65.6)
Febrile neutropenia	14 (43.8)
Increased ALT	4 (12.5)
Increased AST	4 (12.5)
Increased GGT	4 (12.5)
Nausea	4 (12.5)
Increased blood bilirubin	2 (6.3)
Premature menopause	2 (6.3)
Upper abdominal pain	2 (6.3)
Serious treatment-emergent AEs *Reported in ≥ 2 patients*	
Abdominal pain	2 (6.3)
Nausea	2 (6.3)
Drug withdrawal syndrome	2 (6.3)
Vomiting	2 (6.3)

[*]Hematologic AEs commonly observed post-transplantation have been excluded;
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

- 1 patient with a nonserious Grade 2 DP-related neutropenic fever (resolved)
- No cases of veno-occlusive liver disease, no graft failure
- No vector-mediated RCL and no insertional oncogenesis
- One death, attributed to cardiopulmonary disease and unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD burden

[†]Occurred on study day 10 and resolved on study day 19

ACS, acute chest syndrome; AE, adverse event; DP, drug product; LVH, left ventricular hypertrophy; PIs, principal investigators; RCL, replication competent lentivirus; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Clinical hold on bluebird bio studies on LentiGlobin for sickle cell disease (bb1111)

Data in this presentation are accurate as of 20 August 2020

Beyond this data cutoff, two SUSARs were reported in the Phase 1/2 HGB-206 study

Initially reported MDS diagnosis revised to transfusion-dependent anemia in a patient treated in Group C

- Patient had persistent anemia 6 months after transplant and was found to have trisomy 8 in 6% of cells scored on a 6-month bone marrow aspirate but no blasts or dysplastic cells
- A follow-up bone marrow aspirate revealed no genetic or chromosomal abnormalities and no evidence of myeloid neoplasm; the diagnosis was changed to transfusion-dependent anemia with investigations ongoing
- Investigator assessed as serious, Grade 3, ongoing, and possibly related to LentiGlobin for SCD

Patient in Group A diagnosed with AML (treated 5.5 years ago)

- Mutations in genes typically associated with the development of AML, specifically, monosomy 7, *RUNX1,* and *PTPN11*
- Vector insertion in the AML cells took place in the *VAMP4* gene, which has no reported role in cellular proliferation or oncogenesis, and this insertion had no impact on gene expression or gene regulation
- Case is unlikely related to vector-mediated insertional oncogenesis. Investigator assessed it as serious, Grade 4, and possibly related to LentiGlobin for SCD
- The underlying increased risk of hematologic malignancies in SCD, combined with the transplant procedure and associated proliferative stress, as well as continued hematopoietic stress due to minimal clinical benefit in this Group A patient (*DP manufactured using stem cells collected via BMH and using an earlier version of the manufacturing process that led to drug products with low transduction efficiency and resulted in limited clinical benefit*) may have contributed to the development of AML

SUSAR, suspected unexpected serious adverse reactions; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; VAMP4, vesicle-associated membrane protein 4; BM, bone marrow; BMH, bone marrow harvest; DP, drug product.

HGB-206 Group C: Summary

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- Complete resolution of VOEs after stabilization of HbA^{T87Q} expression†, with up to 24 months of follow-up
- Improvement in patient-reported pain intensity sustained over 24 months of follow-up
- Median total Hb is consistently ≥ 11 g/dL ≥ 6 months post-LentiGlobin treatment, with a median anti-sickling HbA^{T87Q} ≥ 40%
- Near pancellular expression of HbA^{T87Q} ≥ 6 months post-LentiGlobin, with, on average, ~90% of RBCs containing HbA^{T87Q} at ≥ 18 months post treatment
- Key markers of hemolysis approaching near-normal levels post-LentiGlobin treatment
- The safety profile post-LentiGlobin for SCD remains generally consistent with the risks of autologous stem cell transplant, myeloablative single-agent busulfan conditioning, and underlying SCD

†HbA^{T87Q} expression stabilizes within 6 months.

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

Thank you to the study site members as well as the study participants and their families

For video

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