Updated Results from the HGB-206 Group C Study of LentiGlobin for Sickle Cell Disease Gene Therapy

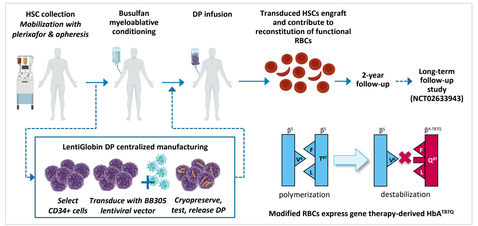
Lakshmanan Krishnamurti[1], Alexis A. Thompson[2,3], Mark C. Walters[4], Janet L. Kwiatkowski[5,6], Markus Y. Mapara[7], Stacey Rifkin-Zenenberg[8], Banu Aygun[9], Kimberly A. Kasow[10], Manfred Schmidt[11], Alex Miller[12], Meghan Gallagher[12], Xinyan Zhang[12], Dennis Kim[12], Sunita Goyal[12], Julie Kanter[13], John F. Tisdale[14]

[1]Aflac Cancer and Blood Disorders Center, Department of Pediatrics, Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [4]UCSF Benioff Children's Hospital, Oakland, CA, USA; [5]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [7]Division of Hematology/Oncology, Columbia Center for Translational Immunology, Columbia University Medical Center, New York, NY, USA; [8]Hackensack University Medical Center, Hackensack, NJ, USA; [9]Cohen Children's Medical Center, Queens, NY, USA; [10]University of North Carolina, Chapel Hill, NC, USA; [11]GeneWerk GmbH, Heidelberg, Germany; [12]bluebird bio, Inc., Cambridge, MA, USA; [13]University of Alabama Birmingham, Birmingham, AL, USA; [14]Cellular and Molecular Therapeutics Branch NHLBI/NIDDK, National Institutes of Health, Bethesda, MD, USA

INTRODUCTION

- Sickle cell disease (SCD) is characterized by high morbidity and early mortality[1]
- Sickled, rigid red blood cells (RBCs) caused by sickle hemoglobin (HbS) polymerization are prone to hemolysis, resulting in chronic hemolytic anemia, vasculopathy, and vaso-occlusive events (VOEs) that contribute to morbidity and early mortality[1–3]
- SCD results in >50% mortality before 45 years of age (with βS/βS genotypes)[2]
- Curative therapies are needed to improve outcomes of patients with SCD
  - <15% of patients with SCD have a human leukocyte antigen (HLA)-matched sibling donor[4,5]
- Gene therapy offers an alternative option to allogeneic hematopoietic stem cell transplantation (HSCT)
- HGB-206 is an ongoing study of LentiGlobin (bb1111) for SCD gene therapy (GT) (**Figure 1**)
  - The largest clinical trial of GT in SCD (N=41) with follow-up of >5 years
- LentiGlobin for SCD gene therapy consists of an autologous CD34+ cell-enriched population from patients with SCD transduced with BB305 lentiviral vector (LVV) encoding the modified $\beta^{A\text{-}T87Q}$-globin gene (**Figure 1**)
- Addition of the modified $\beta^{A\text{-}T87Q}$-globin gene to patients' hematopoietic stem cells (HSCs) results in production of anti-sickling HbA^{T87Q} in order to reduce RBC sickling by intervening at the genetic level
- HbA^{T87Q} is a variant HbA specifically designed with a single amino acid change to give it anti-sickling property, while otherwise maintaining the same morphology and function as naturally occurring HbAs

Figure 1. LentiGlobin for SCD gene therapy overview



DP, drug product; Hb, hemoglobin; HSCs, hematopoietic stem cells; RBCs, red blood cells; SCD, sickle cell disease.

METHODS

- HGB-206 is an open-label, multicenter, phase 1/2 study of LentiGlobin GT (bb1111) in patients with severe SCD (**Table 1**)

Table 1. HGB-206 Group C: Key enrollment criteria and outcomes

Enrollment Criteria	Outcomes
≥ 12 and ≤ 50 years of age	Complete resolution of severe VOEs
βSβS, βSβ0, βSβ+ genotype	Weighted average HbA^{T87Q} ≥ 30% of unsupported total Hb for ≥ 6 months post-DP
History of severe VOEs*	Weighted average: unsupported total Hb increase ≥ 3 g/dL vs baseline or total Hb ≥ 10 g/dL for ≥ 6 months post-DP
Hydroxyurea failure or intolerance	
Enrollment Completed (NCT02140554)	

*Per inclusion criteria, severe VOEs include hospitalization or emergency room (ER) visit ≥ 24 hours or ≥ 2 visits to a day unit or ER over 72 hours, both requiring intravenous 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; Hb, hemoglobin; VOE, vaso-occlusive event.

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RESULTS

- As of August 20, 2020, 43 patients had undergone cell collection (**Table 2**)
  - Median (minimum [min]– maximum [max]) age was 24 (12–38) years and 58% of patients were male (n=25)
- A total of 32 patients were treated with LentiGlobin (**Table 3**)
  - Patients were followed for a median of 13.0 (min–max: 1.1–30.9) months

Table 2. HGB-206 Group C Patient characteristics (ITT)

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 Female Male	 **18** **25**
Genotype, n β^S/β^S β^S/β^0 β^S/β^+	 **40** **2** **1**
SCD history	
Severe VOEs*, n Annualized number of events, median (min–max)	**39** **3.5** (0.5–16.0)
ACS, n Annualized number of events, median (min–max)	**10** **0.5** (0.5–1)
Priapism, n	**2**
Any history of stroke, n	**6**

ACS, acute chest syndrome; ITT, intent to treat; max, maximum; min, minimum; SCD, sickle cell disease; VOE, vaso-occlusive event.

Table 3. HGB-206 Group C: Treatment and drug product characteristics (transplant)

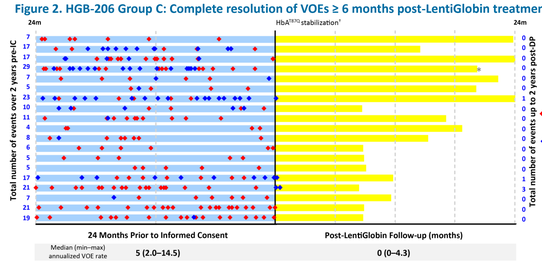
Parameter	N=32 Median (min–max)
Treatment characteristics	
Mobilization cycles, n	**2** (1–4)
CD34+ cells collected per mobilization cycle, $x10^6$ cells/kg	**10.4** (3.9–55.4)
Estimated average busulfan AUC, min*µmol†	**4843** (1445‡–7322)
Neutrophil engraftment, ANC ≥ 500 /µl x 3 days, days	**19.5** (12–35)
Platelet engraftment, platelets > 50k /µl x 3 days, days§	**30** (18–136)
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.

Efficacy

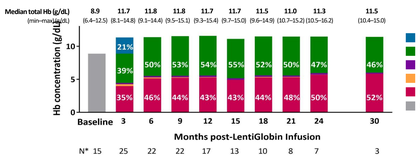
- Complete resolution of severe VOEs with up to 24 months of follow-up (**Figure 2**)
- Complete resolution of VOEs after stabilization of HbAT87Q expression within 6 months, with up to 24 months of follow-up
- Median total Hb was consistently ≥ 11 g/dL ≥ 6 months post-LentiGlobin treatment, with a median anti-sickling HbAT87Q ≥ 40% (**Figure 3**)
- In patients with ≥ 6 months of follow-up, median total Hb increased from 8.9 g/dL at baseline to ≥ 11.8 g/dL at Month 6
- At the last visit in adolescents with ≥ 6 months of follow-up (n=6), median total Hb and HbA^{T87Q} were 13.5 g/dL and 6.1 g/dL, respectively
- Near pancellular expression of HbA^{T87Q} was observed ≥6 months post-treatment with ~90% of RBCs containing $\beta^{A\text{-}T87Q}$ by 18 months (n=10) (data not shown)
- Median (min–max) HbA^{T87Q}/RBC was 15.3 (11.7–20) pg in patients with ≥ 6 months follow-up, which is comparable to the 13–18 pg of HbA/RBC in individuals with sickle cell trait, and higher than 10 pg of HbF/RBC in those with hereditary persistence of HbF (HPFH) (data not shown)
- Key markers of hemolysis approached near-normal levels post-LentiGlobin treatment (**Figure 4**)

Figure 2. HGB-206 Group C: Complete resolution of VOEs ≥ 6 months post-LentiGlobin treatment



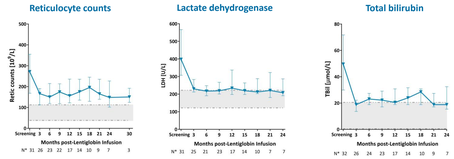
Protocol VOEs are shown. Patients with ≥ 4 sVOEs at baseline before IC and with ≥ 6 months of follow-up post-DP infusion were included. A VOE includes episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than 2 hours and severe enough to require care at a medical facility. A VOE includes acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration.
†HbAT87Q 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; max, maximum; min, minimum; VOC, vaso-occlusive crisis; VOE, vaso-occlusive event.

Figure 3. HGB-206 Group C: Median HbA^{T87Q} ≥ 40% at ≥ 6 months post-LentiGlobin treatment



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

Figure 4. HGB-206 Group C: Hemolysis markers approaching near-normal levels post-LentiGlobin treatment

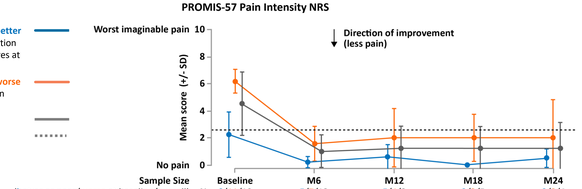


Median (quartile 1, quartile 3) depicted; dot-dash lines denote lower and upper limits of normal values. *Number of patients with data available.
LDH, lactate dehydrogenase; Retic, reticulocyte; Tbil, total bilirubin.

Patient-reported outcomes

- Overall mean PROMIS-57 pain intensity scores decreased from 4.5 at baseline (n=19) to 1.3 at Month 24 (n=4) (**Figure 5**)

Figure 5. HGB-206 Group C: Decrease in patient-reported pain intensity



Patients with baseline values:	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 May, 2021. NRS, Numeric Rating Scale; PROMIS, Patient Reported Outcomes Measurement Information System.
M, month; SD, standard deviation.

Safety

- The safety profile post-LentiGlobin for SCD GT remains generally consistent with risk of autologous stem cell transplant, myeloablative single-agent busulfan conditioning, and underlying SCD (**Table 4**)
- One patient had a non-serious Grade 2 DP-related adverse event (AE; febrile neutropenia)†
- No cases of veno-occlusive liver disease
- No graft failure
- No vector-mediated replication competent lentivirus and no insertional oncogenesis
- One death, unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD burden
  - A 27-year-old patient with history of VOC/ACS (14 episodes/year), pulmonary hypertension, and venous thrombosis died following a cardiac arrest ~20 months post treatment
  - Autopsy showed cardiac biventricular dilation with concentric LVH and moderate cardiac interstitial fibrosis; there was no evidence of pulmonary embolism or stroke
  - Per principal investigator assessment, the patient's sudden death appeared to be associated with cardiac fibrosis and other chronic organ injury

Table 4. HGB-206 Group C: Non-hematologic treatment-emergent AEs and serious treatment-emergent AEs

Treatment-emergent Grade ≥ 3 AEs, n (%) *Reported in ≥ 2 patients**	N=32
Stomatitis	21 (65.6)
Febrile neutropenia	14 (43.8)
Increased ALT	4 (12.5)
Increased AST	4 (12.5)
Increased GGT	4 (12.5)
Increased blood bilirubin	2 (6.3)
Nausea	4 (12.5)
Premature menopause	2 (6.3)
Upper abdominal pain	2 (6.3)
Serious treatment-emergent AEs, n (%) *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; †Occurred on study day 10 and resolved on study day 19.
ACS, acute chest syndrome; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DP, drug product; GGT, gamma-glutamyl transferase; LVH, left ventricular hypertrophy; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

HGB-206 clinical trial hold following serious adverse reactions (SUSARs) in HGB-206 study

- Beyond the 20 Aug 2020 data cut, two suspected unexpected SUSARs were reported and as of February 2021, HGB-206 is on a clinical hold
  - **Group C:** Initially reported trisomy 8/**myelodysplastic syndrome diagnosis revised to transfusion-dependent anemia** and investigation is ongoing. Investigator assessed as serious, Grade 3, ongoing, and possibly related to bb1111
  - **Group A:** Patient diagnosed with **acute myeloid leukemia** > 5 years post-LentiGlobin treatment. Investigator assessed as serious, Grade 4, ongoing, and possibly related to bb1111

SUMMARY

- Complete resolution of severe VOEs was observed in all patients
- LentiGlobin for SCD GT increased total Hb expression, while lowering HbS expression and resulted in near pancellular $\beta^{A\text{-}T87Q}$ expression, which impacts the pathophysiology of SCD as demonstrated by reduced RBC sickling, hemolysis, and erythropoiesis
- The safety profile post-LentiGlobin for SCD GT remains generally consistent with risk of autologous stem cell transplant, myeloablative single-agent busulfan conditioning, and underlying SCD

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DISCLOSURES

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