ASH 2017 Abstract #4609

Longer-Term Follow-up on the First Patients with Severe Hemoglobinopathies Treated with LentiGlobin™ Gene Therapy

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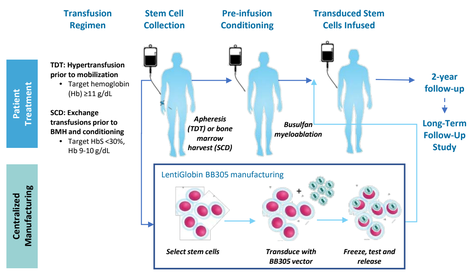
INTRODUCTION

- β-globin gene addition into hematopoietic stem cells (HSCs) has the potential to reduce or eliminate the symptoms of severe sickle cell disease (SCD) and reduce or eliminate transfusion requirements in transfusion-dependent β-thalassemia (TDT)
- LentiGlobin contains autologous CD34+ cells transduced with the BB305 lentiviral vector, which encodes a human β-globin gene containing a single point mutation (AT87Q) designed to confer anti-sickling properties similar to those observed with γ-globin
- Proof of concept using lentiviral β-globin gene addition for treatment of patients with TDT has been established[1] and LentiGlobin treatment in patients with severe SCD or TDT has been previously reported from this study, HGB-205[2,3]

STUDY DESIGN

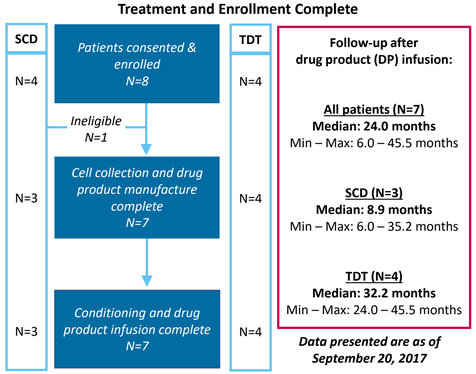


METHODS

- Patients (5–35 years of age) with severe SCD (e.g. ≥2 acute chest syndrome [ACS] episodes or ≥2 vaso-occlusive crises [VOC] in preceding year/in year prior to regular transfusions) or TDT (≥100mL/kg of packed red blood cells [pRBCs] per year) were enrolled
- Following mobilization and apheresis (TDT) or bone marrow harvest (SCD), autologous CD34+ cells were transduced with the BB305 lentiviral vector
- Patients underwent myeloablative conditioning with busulfan prior to infusion of the transduced cells
- After infusion, patients were monitored for hematologic engraftment, vector copy number (VCN), HbA^{T87Q} expression, transfusion requirements (TDT), VOCs and hospitalizations (SCD), adverse events (AEs) and integration site analysis

STUDY STATUS

Treatment and Enrollment Complete



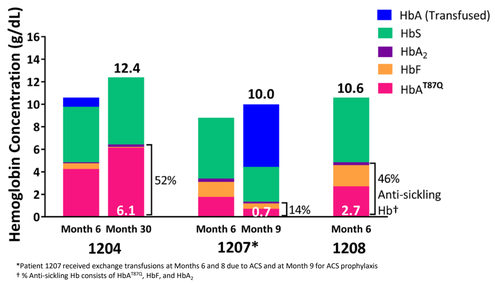
RESULTS: SEVERE SICKLE CELL DISEASE (SCD)

Patient and DP characteristics

Patient	1204	1207	1208
Age at Enrollment (years)	13	16	21
Genotype	β^S/β^S	β^S/β^S	β^S/β^0
Busulfan AUC† (daily average, μM*min)	4,841	5,022	5,447
VCN in Drug Product	1.2/1.0	0.7/1.0	0.8/0.5
CD34+ Cell Dose (x10^6/kg)	5.6	4.7	3.0
Follow-up (months)	35.2	8.9	6.0

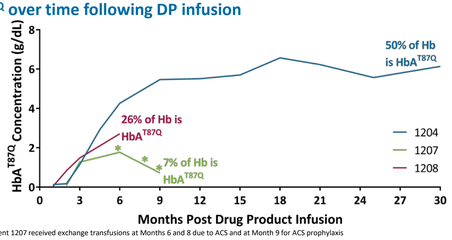
VCN: number of vector copies per diploid genome
† Busulfan plasma levels were monitored daily and busulfan dose was adjusted to meet the daily target average AUC of 4000-5200 μM*min

Hb at 6 months and most recent study visit



*Patient 1207 received exchange transfusions at Months 6 and 8 due to ACS and at Month 9 for ACS prophylaxis
† % Anti-sickling Hb consists of HbA^{T87Q}, HbF, and HbA_2

HbA^{T87Q} over time following DP infusion



*Patient 1207 received exchange transfusions at Months 6 and 8 due to ACS and at Month 9 for ACS prophylaxis

- All patients treated show a rising trajectory of HbA^{T87Q} production through 6 months
- HbA^{T87Q} in patient 1204 remained stable after 9 months post-infusion
- Decrease in HbA^{T87Q} levels in patient 1207 followed exchange transfusions

VOC and ACS prior to and following DP infusion

Patient	Past Medical History	Post-DP Infusion
1204	• VOCs (1-3/yr) and ACS (x2) despite hydroxyurea • Bilateral hip osteonecrosis, cholecystectomy and splenectomy for hypersplenism • A RBC transfusion program was initiated in 2010, including iron chelation*	Approximately 30 months post-treatment, the patient suffered an episode of acute gastroenteritis with a 2-day fever of up to 40°C, leading to dehydration; the patient subsequently developed a VOC and was hospitalized for 7 days for symptomatic treatments
1207	• VOCs (up to 7/yr) despite hydroxyurea and ACS (x5) • Regular prophylactic RBC transfusions initiated in 2013*; iron chelation was started 5 months later	Patient, who has restrictive pulmonary syndrome, had 2 episodes of ACS • Events occurred approximately 6 and 8 months after DP infusion • Both resulted in hospitalizations, treated with exchange transfusions Patient received a prophylactic exchange transfusion at Month 9 and has since been receiving HU and nightly oxygen with no subsequent relapse
1208	• VOCs (up to 5/year) and ACS (x6) • In the absence of hydroxyurea efficacy, regular prophylactic RBC transfusions were initiated in 2014* • Despite regular transfusions, patient was still symptomatic with 2 VOC and 1 ACS	• No episodes of VOCs, ACS, pain, hemolysis, or concomitant treatments

*According to treating physician records

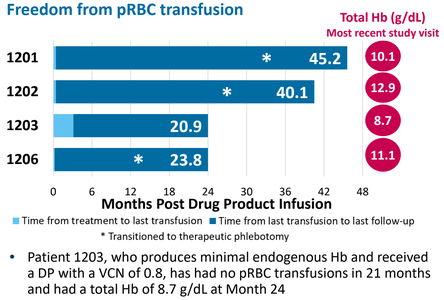
RESULTS: TRANSFUSION-DEPENDENT β-THALASSEMIA (TDT)

Patient and DP characteristics

Patient	1201	1202	1203	1206
Age at Enrollment (years)	18	16	19	17
Genotype	β^0/β^E	β^0/β^E	homozygous IVS1 nt 110 G>A	β^0/β^E
Pre-Treatment pRBC Transfusions† (mL/kg/yr)	139	188	176	197
Busulfan AUC‡ (daily average, μM*min)	4967	5212	4670§	4930
VCN in Drug Product	1.5	2.1	0.8	1.1
CD34+ Cell Dose (x10^6/kg)	8.9	13.6	8.8	12.0
Follow-up (months)	**45.5**	**40.5**	**24.0**	**24.0**

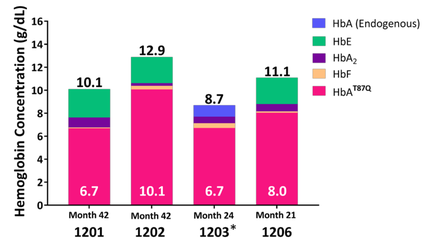
VCN = number of vector copies per diploid genome
† Mean pRBC requirement per year, over the past 2 years prior to consent
‡ Busulfan plasma levels were monitored daily and busulfan dose was adjusted to meet the daily target average AUC of 4000-5200 μM*min
§ Patient 1203 was the only patient who did not require an increased busulfan dose to achieve target AUC

Freedom from pRBC transfusion



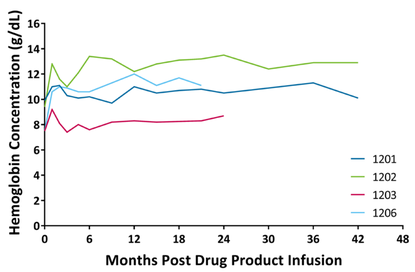
- Patient 1203, who produces minimal endogenous Hb and received a DP with a VCN of 0.8, has had no pRBC transfusions in 21 months and had a total Hb of 8.7 g/dL at Month 24

Hb at most recent study visit

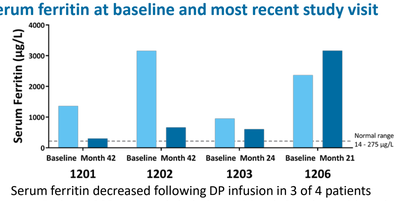


*HbA produced by patient 1203 is a result of the patient's IVS1 nt 110 G>A genotype

Hb over time following DP infusion

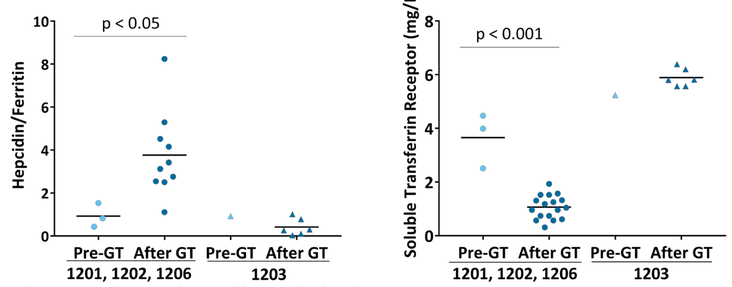


Serum ferritin at baseline and most recent study visit



- Serum ferritin decreased following DP infusion in 3 of 4 patients
  - Patient 1202 restarted chelation at Month 9 and transitioned to phlebotomy, however has been able to discontinue both
  - Patient 1201 was on chelation Month 3 – 30 and began phlebotomy at Month 33
  - Patient 1203 restarted chelation therapy at Month 15
  - Patient 1206 began phlebotomy at Month 13

Markers of dyserythropoiesis have largely returned to normal in 3 of 4 patients



GT, gene therapy; Horizontal bars represent medians; p-values calculated using two-sided Wilcoxon rank-sum test

- Following gene therapy, sTFR decreased in 3 β^E/β^0 patients ($p<0.001$), while hepcidin/ferritin ratios increased ($p=0.014$)
- No change was observed for either marker in patient 1203 (homozygous IVS1-110)

SAFETY IN SCD AND TDT TREATED PATIENTS

- Adverse events generally consistent with myeloablative conditioning
  - Non-hematologic Grade 3-4 AEs from conditioning to last follow-up:
    - Stomatitis (n=4), elevated AST (n=2), and one case each of elevated ALT, elevated GGT, elevated hepatic enzymes, premature menopause, tooth infection, oral herpes, major depressive disorder, staphylococcus test positive, cholestasis, hypercapnia, ACS, and pyrexia
- No drug product-related AEs
- 11 serious AEs (SAEs) post-LentiGlobin
  - 3 SAEs related to SCD in 2 patients
    - 2 episodes of ACS in 1 patient and 1 episode of VOC in 1 patient
  - 8 additional SAEs were reported in 5 patients
    - Elevated LFTs, staphylococcus infection, pneumonia, major depressive disorder, wisdom tooth infection, cholestasis, rheumatoid pain, knee pain
- No replication competent lentivirus or evidence of insertional oncogenesis detected to date

SUMMARY

- All patients with severe SCD and TDT continue to successfully produce HbA^{T87Q}
- In patients with SCD
  - Patients are able to produce 14-52% anti-sickling Hb
  - Patient 1204, with more than 30 months follow-up, continues to show marked clinical improvement
- In patients with TDT
  - Patients have been free of chronic transfusions with near normal and stable levels of total Hb
  - 3 of 4 patients have been able to transition to phlebotomy and have had markers of dyserythropoiesis return to near normal levels
- Safety profile of LentiGlobin in this study continues to appear consistent with myeloablative conditioning, with no LentiGlobin related AEs to date
- Three clinical studies are ongoing to further evaluate the safety and efficacy of LentiGlobin:
  - SCD: HGB-206 (NCT02140554)
  - TDT: Northstar-2 (NCT02906202) and Northstar-3 (NCT03207009)

REFERENCES

1) Cavazzana-Calvo M, et al. *Nature*. 2010;467(7313):318-22; **2)** Ribeil JA, et al. *N Engl J Med* 2017; 376:848-855; **3)** Ribeil JA, et al. EHA Learning Center. June 2017; 181918. Abstract P631

ACKNOWLEDGEMENTS

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DISCLOSURES

Dr. Cavazzana has no disclosures to report

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