ASH 2019 Abstract #3358

Results from the Completed HGB-205 Trial of LentiGlobin for β-thalassemia and LentiGlobin for Sickle Cell Disease 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 sickle cell disease (SCD) and reduce or eliminate transfusion requirements in transfusion-dependent β-thalassemia (TDT)
- LentiGlobin for SCD gene therapy contains autologous CD34+ cells from SCD patients transduced with the BB305 lentiviral vector (LVV), encoding human β-globin with an anti-sickling T87Q substitution (HbA^{T87Q})
- Betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) contains autologous CD34+ cells from TDT patients transduced with the BB305 LVV encoding human β-globin gene with a T87Q substitution. $\beta^{A\text{-}T87Q}$-globin combines with α-globin to produce functional gene therapy-derived adult hemoglobin, HbA^{T87Q}
- The proof of concept for beti-cel in patients with TDT and LentiGlobin for SCD was established in the recently completed HGB-205 study (NCT02151526)
- Herein, we provide the safety and efficacy outcomes and long-term follow-up data for 4 patients with TDT and 3 patients with SCD treated in HGB-205

Key eligibility criteria and outcomes

Phase 1/2 study of autologous CD34+ stem cells encoding $\beta^{A\text{-}T87Q}$-globin gene

Key eligibility criteria

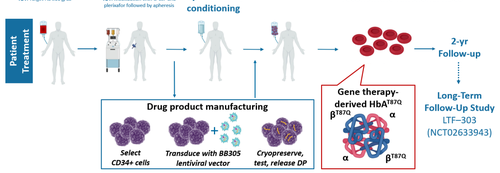
- 5 – 35 years of age
- Eligible for allogeneic HSCT but without a suitable, willing, 10/10 matched HLA-identical sibling donor
- Severe sickle cell disease (e.g., ≥ 2 ACS episodes or ≥ 2 VOC in the preceding year or the year before regular transfusions)
  OR
- Transfusion-dependent β-thalassemia (≥ 100 mL/kg/year of pRBCs in each of the 2 years prior to enrollment)

Key outcomes

- Engraftment, AEs, HbA^{T87Q} levels, and other hematologic and clinical parameters

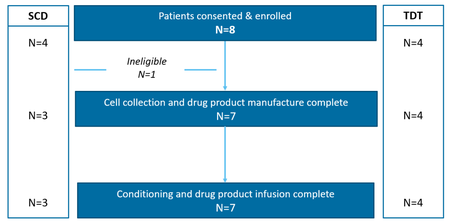
ACS, acute chest syndrome; AE, adverse event; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; pRBC, packed red blood cells; VOC, vaso-occlusive crisis

STUDY DESIGN



DP, drug product; G-CSF, granulocyte colony-stimulating factor; HSC, hematopoietic stem cell; RBC, red blood cell

STUDY DISPOSITION



Study Status

All 7 patients have completed the 2-year HGB-205 study and enrolled in long-term follow-up study, LTF-303 (NCT02633943)

Follow-up after drug product infusion

	SCD (N=3)	TDT (N=4)
Median (Min-Max in months)	28.5 months (25.5 – 52.5)	49.6 months (40.5 – 60.6)

Data presented are as of June 2019

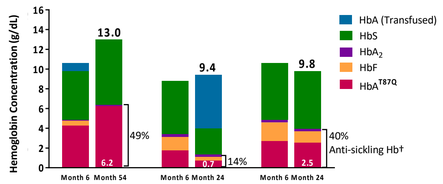
RESULTS: SEVERE SICKLE CELL DISEASE

Table 1. SCD patient and treatment characteristics

Patient characteristics	Pt 1	Pt 2	Pt 3
Age at enrollment (years)	13	16	21
Genotype	β^S/β^S with a single 3.7-kb α-globin gene deletion	β^S/β^S	β^S/β^0
Treatment characteristics			
Busulfan AUC† daily average, μM*min	4,841	5,022	5,447
Drug product VCN vector copies/diploid genome	1.2/1.0‡	0.7/1.0‡	0.8/0.5‡
Drug product cell dose x10^6 CD34+ cells/kg	5.6	4.7	3.0
Follow-up (months)	52.5	28.5	25.5

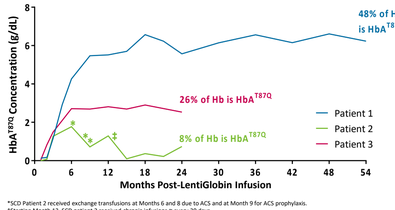
AUC, area under the curve; VCN, vector copy number (number of vector copies per diploid genome)
†Busulfan plasma levels were monitored daily and busulfan dose was adjusted to meet the daily target average AUC of 4000 – 5200 μM*min
‡Corresponds to 2 drug products from 2 separate bone marrow harvests per patient

Figure 1. HbS ≤ 60% at ≥ 6 months post-LentiGlobin treatment in the 2 patients with SCD off-transfusion



*Patient 2 received exchange transfusions at Months 6 and 8 due to ACS and at Month 9 for ACS prophylaxis. Starting Month 13, patient 2 received chronic infusions ~ every 30 days
†Anti-sickling hemoglobin consists of HbA^{T87Q}, HbF, and HbA_2

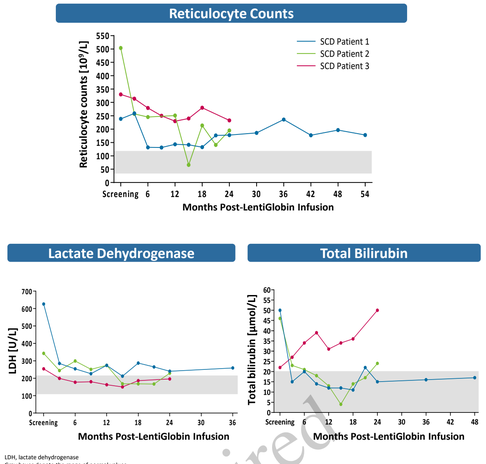
Figure 2. HbA^{T87Q} levels remain stable post-LentiGlobin treatment in the 2 patients with SCD off-transfusion



*SCD Patient 2 received exchange transfusions at Months 6 and 8 due to ACS and at Month 9 for ACS prophylaxis.
†Starting Month 13, SCD patient 2 received chronic infusions ~ every 30 days

- All treated patients show a rising trajectory of HbA^{T87Q} expression through 6 months
- In patients 1 and 3, who were no longer on transfusions since month 3 and month 1, respectively, HbA^{T87Q} expression remained stable for up to 4.5 years following LentiGlobin treatment
- Patient 2 received exchange transfusions at months 6 and 8 due to ACS and at month 9 for ACS prophylaxis. Starting month 13, patient 2 received chronic infusions ~ every 30 days. In patient 2, decrease in HbA^{T87Q} level followed exchange transfusions

Figure 3. Hemolysis markers post-LentiGlobin treatment



LDH, lactate dehydrogenase
Gray boxes denote the range of normal values

Table 3. Safety of LentiGlobin for SCD is generally consistent with myeloablative busulfan conditioning

Subjects with Non-hematologic ≥ Grade 3 AEs* *Post-LentiGlobin infusion up to 2 years of follow-up*	N=3
Acute chest syndrome	1
Abdominal pain	1
Cholestasis	1
Hepatic enzyme increased	1
Pyrexia	1
Staphylococcus test positive	1
Subjects with SAEs† *Post-LentiGlobin infusion in ≥ 2 patients up to last follow-up*	
Vaso-occlusive crisis	2
Hepatic enzyme elevation	2

*Hematologic AEs commonly observed post-transplant have been excluded
†SAEs reported in 1 patient post-LentiGlobin infusion: ACS, acute back pain, rheumatoid pain, knee pain, procedural pain, cholestasis, vasovagal episode, flu syndrome, infection/infestation - Staphylococcal bacteraemia

- No LentiGlobin-related AEs
- No cases of veno-occlusive liver disease
- No graft failure or deaths reported
- No vector-mediated replication-competent lentivirus
- No evidence of clonal dominance

Table 2. VOCs and ACS post-LentiGlobin treatment in patients with SCD

Patient	Patient 1	Patient 2	Patient 3
Past Medical History	• VOCs (up to 3/year) and ACS (x2) despite hydroxyurea • Bilateral hip osteonecrosis, cholecystectomy, splenectomy • An RBC transfusion program was initiated in 2010, including iron chelation treatment*	• VOCs (up to 7/year) despite hydroxyurea and ACS (x5) • Tonsillectomy, cholecystectomy, osteonecrosis • An RBC transfusion program was initiated in 2013*; including iron chelation	• VOCs (up to 5/year) and ACS (x6) • Cholecystectomy, splenectomy • An RBC transfusion program was initiated in 2014*; iron chelation was started ~1 year later • Despite regular transfusions, patient was still symptomatic with 2 VOC and 1 ACS
Post-Drug Product Infusion	• Approximately 30 months post-LentiGlobin treatment, the patient experienced 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.	• Patient, who has restrictive pulmonary syndrome, had 2 episodes of ACS approximately 6 and 8 months after LentiGlobin treatment. Both ACS episodes resulted in hospitalization and were treated with exchange transfusions • Patient resumed chronic pRBC transfusions and hydroxyurea treatment at Month 13 and subsequently experienced 2 SAEs of vaso-occlusive pain; no additional SAEs of vaso-occlusive pain or ACS were reported during the last 16 months of follow-up post-LentiGlobin treatment	• No episodes of VOCs or ACS during 25.5 months of follow-up post-LentiGlobin treatment

*According to treating physician records
SAE, serious adverse event

RESULTS: TRANSFUSION-DEPENDENT β-THALASSEMIA

Table 4. Patient and treatment characteristics

Patient characteristics	Pt 1	Pt 2	Pt 3	Pt 4
Age at enrollment (years)	18	16	19	17
Genotype	β^0/β^E	β^0/β^E	β^+ IVS-I-110/ β^+ IVS-I-110	β^0/β^E
Treatment characteristics				
Busulfan AUC† daily average, μM*min	4967	5212	4670‡	4930
Drug product VCN vector copies/diploid genome	1.5	2.1	0.8	1.1
Drug product cell dose x10^6 CD34+ cells/kg	8.9	13.6	8.8	12.0
Follow-up (months)	58.6	60.6	40.5	40.5

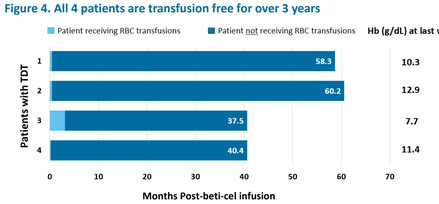
†Busulfan plasma levels were monitored daily and busulfan dose was adjusted to meet the daily target average AUC of 4000 – 5200 μM*min
‡TDT Patient 3 was the only patient who did not require an increased busulfan dose to achieve target AUC

Table 5. Pre-study pRBC Transfusion history

	Pt 1	Pt 2	Pt 3	Pt 4
Volume mL/kg/yr	139	188	176	197
Number n/yr	10.5	12	13	13
Pre-transfusion Hb g/dL	8.2	10.6	8.1	10.8

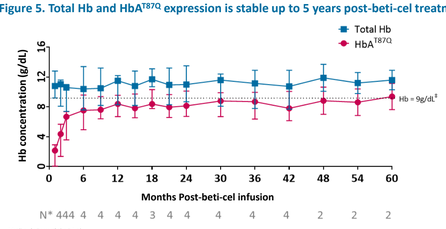
pRBC, packed red blood cells
Retrospective data 2-years prior to study enrollment

Figure 4. All 4 patients are transfusion free for over 3 years



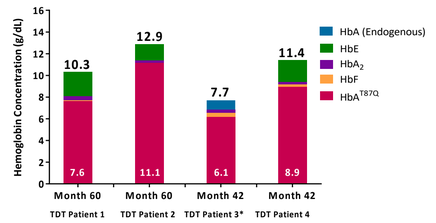
- 3/4 patients achieved transfusion independence (weighted average Hb ≥ 9 g/dL without any RBC transfusions for ≥ 12 months) for a median duration of 56.3 (38.2 - 57.6) months
- TDT Patient 3 has been off transfusions for 37.5 months and had total Hb of 7.7 g/dL at last visit, which was below the ≥ 9 g/dL requirement of transfusion independence as defined above

Figure 5. Total Hb and HbA^{T87Q} expression is stable up to 5 years post-beti-cel treatment



Median (min,max) depicted
*Shows number of patients for whom data are available
‡transfusion independence is defined in the protocol as weighted average Hb ≥ 9 g/dL in addition to RBC transfusions for ≥ 12 months

Figure 6. HbA^{T87Q} levels contributed to 74% – 87% of the total Hb



*HbA produced by TDT Patient 3 is a result of the patient's IVS1 nt 110 G>A genotype

Figure 7. Dyserythropoiesis markers post-beti-cel treatment

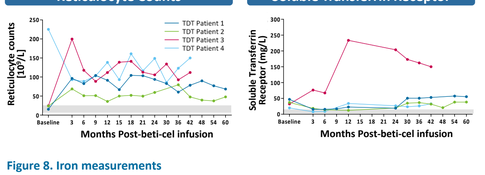
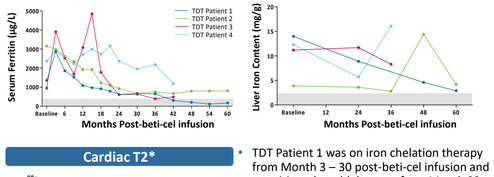
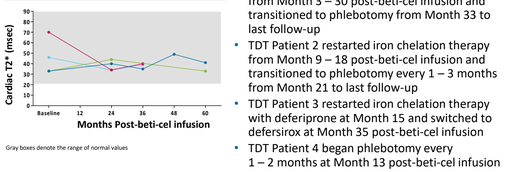


Figure 8. Iron measurements





Gray boxes denote the range of normal values

- TDT Patient 1 was on iron chelation therapy from Month 3 – 30 post-beti-cel infusion and transitioned to phlebotomy from Month 33 to last follow-up
- TDT Patient 2 restarted iron chelation therapy from Month 9 – 18 post-beti-cel infusion and transitioned to phlebotomy every 1 – 3 months from Month 21 to last follow-up
- TDT Patient 3 restarted iron chelation therapy with deferiprone at Month 15 and switched to defersirox at Month 35 post-beti-cel infusion
- TDT Patient 4 began phlebotomy every 1 – 2 months at Month 13 post-beti-cel infusion

Table 6. Safety of beti-cel treatment is generally consistent with myeloablative busulfan conditioning

Subjects with Non-hematologic* ≥ Grade 3 AEs† *Post-beti-cel infusion up to 2 years of follow-up*	N=4
Stomatitis	3
Aspartate aminotransferase increased	2
Alanine aminotransferase increased	1
Gamma-glutamyltransferase increased	1
Major depression	1
Oral herpes	1
Premature menopause	1
Tooth infection	1

Subjects with SAEs *Post-beti-cel infusion up to last follow-up*	
Wisdom tooth infection	1
Pneumonia	1
Major depressive disorder	1

*Hematologic AEs commonly observed post-transplantation have been excluded
†No grade 4 or 5 non-hematologic events were reported

- **No beti-cel-related AEs**
- **No graft failure or deaths reported**
- **No vector-mediated replication-competent lentivirus**
- **No evidence of clonal dominance**

SUMMARY

- Patients with SCD have been followed for up to 4.5 years post-LentiGlobin gene therapy
  - Robust expression of HbA^{T87Q} and HbS ≤ 60% with ≥ 6 months of follow-up post-LentiGlobin treatment in the 2 patients off transfusion
  - Reduction in hemolysis and in VOCs plus ACS post-LentiGlobin treatment in the 2 patients off transfusion
- Patients with TDT have been followed for up to 5 years post-beti-cel (LentiGlobin for β-thalassemia) gene therapy
  - All 4 patients are transfusion free
  - Total Hb, driven by sustained production of HbA^{T87Q}, is stable up to 5 years post-beti-cel treatment
  - Three patients who had restarted iron chelation therapy were able to stop and transition to phlebotomy for iron reduction
- The safety profile of LentiGlobin for SCD and beti-cel for TDT in HGB-205 is generally consistent with myeloablative conditioning, with no drug product-related AEs to date
- Clinical studies are ongoing to further evaluate the safety and efficacy of:
  - LentiGlobin for SCD: HGB-206 (NCT02140554)
  - beti-cel: Northstar-2 (NCT02906202) and Northstar-3 (NCT03207009)

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DISCLOSURES

Dr. Magrin has no disclosures to report