UPDATE ON THE FIRST PATIENTS WITH SEVERE HEMOGLOBINOPATHIES TREATED WITH LENTIGLOBIN GENE THERAPY

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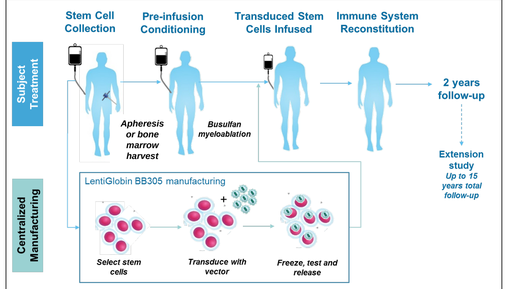
INTRODUCTION

LentiGlobin™ Drug Product (DP) contains autologous CD34+ cells transduced with the BB305 lentiviral vector, which encodes a human β-globin gene containing a single point mutation (A^{T87Q}) designed to confer anti-sickling properties similar to those observed with γ-globin. We previously reported proof of concept for LentiGlobin DP treatment in a single patient with severe sickle cell disease (SCD) and from 4 treated patients with transfusion-dependent β-thalassemia (TDT). Here, we provide an update on these 5 patients as well as early data from a further 2 treated SCD patients.

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 [RBCs] per year) were enrolled. Following mobilization and apheresis (for TDT) or bone marrow harvest (for 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), and HbA^{T87Q} expression. Disease-specific assessments included transfusion requirements for TDT, or VOCs and hospitalizations for SCD. Safety assessments included adverse events (AEs) and integration site analysis. Data are reported as of **June 2nd, 2017.**

STUDY STATUS

Patients consented & enrolled N=8

Ineligible N=1

Cell collection and drug product manufacture complete N=7

Conditioning and drug product infusion complete N=7

Follow-up after drug-product infusion for 7 treated patients (4 TDT, 3 SCD)

Median: 23.4 months range: 3.4 – 42.2 months

As of June 2, 2017

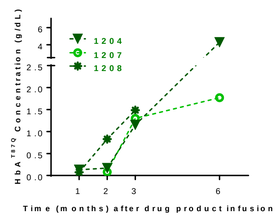
RESULTS: Severe Sickle Cell Disease (SCD)

Patient and DP Characteristics

	1204	1207	1208
Age at Enrollment (yrs)	13	16	21
Genotype	β^S/β^S	β^S/β^S	β^S/β^0
Busulfan AUC (average, μM*min)	4,841	5,022	5,447
CD34+ Cell Dose ($x10^6$/kg)	5.6	4.7	3.0
VCN in Drug Product[1]	1.0/1.2	0.7/1.0	0.8/0.5
Follow-up (months)	31.7	6.1	3.4
Neutrophil engraftment[2]	Day + 38	+ 27	+32
Platelet engraftment[3]	Day + 92	+ 51	+39

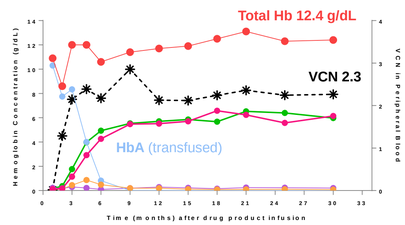
1. VCN: number of vector copies per diploid genome; 2. Absolute neutrophil count [AUC] ≥ 500 cells/μL for 3 consecutive days; 3. Unsupported platelet count ≥ 50,000/μL for 3 consecutive measures.

HbA^{T87Q} Production



One patient with severe SCD was treated in October 2015. The second and third patients with severe SCD were treated in December 2016 and March 2017. All 3 patients treated show a rising trajectory of therapeutic hemoglobin HbA^{T87Q} production through 6 months or last follow up.

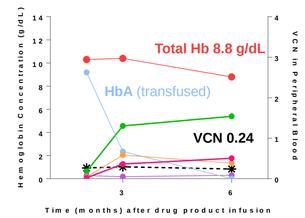
Patient 1204 (31.7 months follow up)



HbA^{T87Q} 50% HbS 48% HbA_2 2% HbF <1%

Patient had a history of VOCs (1-3/yr) and ACS (x2) despite hydroxyurea (HU); he had bilateral hip osteonecrosis and had undergone a cholecystectomy and splenectomy; a transfusion program was initiated in 2010, including iron chelation*. The patient had his last RBC transfusion on Day 88 post-treatment. 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. Subsequently, the patient developed a VOC and was hospitalized. His HbA^{T87Q} and peripheral blood VCN levels have remained stable (T87Q 6.1 g/dL, VCN 2.3 at 30 months). Pre-treatment and most recent (Month 24) laboratory values: reticulocytes 238.3 x 10^9/L and 177.6 x 10^9/L; LDH 626 U/L and 240 U/L; and bilirubin 50 μmol/L and 15 μmol/L.

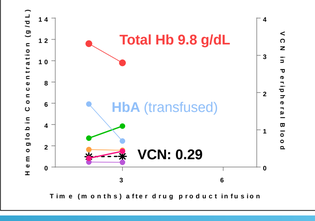
Patient 1207 (6.1 months follow up)



HbA^{T87Q} 20% HbS 61% HbF 15% HbA_2 3%

Patient had a history of VOCs (up to 7/yr) and ACS (x5) despite HU; regular prophylactic RBC transfusions were initiated in 2013*. The patient had her last RBC transfusion on Day 21 post-treatment. Approximately 6 months after treatment, the patient experienced an episode of ACS and was hospitalized. HbA^{T87Q} was 1.8 g/dL at 6 months. Pre-treatment and most recent (Month 6) laboratory values: reticulocytes 333 x 10^9/L and 245.2 x 10^9/L; LDH 343U/L and 299 U/L; and bilirubin 55 μmol/L and 21 μmol/L.

Patient 1208 (3.4 months follow up)



HbA^{T87Q} 15% HbS 39% HbF 16% HbA_2 5% HbA 25%

Patient had a history of VOCs (up to 5/year) and ACS (x6); in the absence of HU efficacy, regular prophylactic RBC transfusions were initiated in 2014*. The patient had her last RBC transfusion on Day 15 post-treatment. HbA^{T87Q} was 1.5 g/dL at 3 months. Pre-treatment and most recent (Month 3) laboratory values: reticulocytes 746.4 x10^9/L and 313.8 x 10^9/L; LDH 254 U/L and 199 U/L; and bilirubin 22 μmol/L and 27 μmol/L.

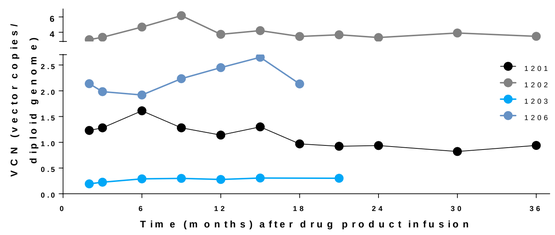
RESULTS: Transfusion-dependent β-thalassemia (TDT)

TDT Patient and DP Characteristics

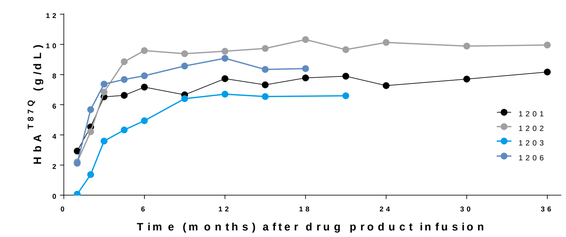
	1201	1202	1203	1206
Age at Enrollment (yrs)	18	16	19	17
Genotype	β^0/β^E	β^0/β^E	homozygous IVS1 nt 110 G>A	β^0/β^E
Pre-Treatment pRBC Transfusions (mL/kg/yr)[1]	139	188	176	189
VCN in Drug Product[2]	1.5	2.1	0.8	1.1
CD34+ Cell Dose ($x10^6$/kg)	8.9	13.6	8.8	12.0
Busulfan AUC (average, μM*min)	4,967	5,212	4,670	4,930
Follow-up (months)	**42.2**	**39.0**	**23.4**	**20.4**

[1]mean pRBC requirement per year, over the past 2 years prior to consent; [2]VCN = number of vector copies per diploid genome

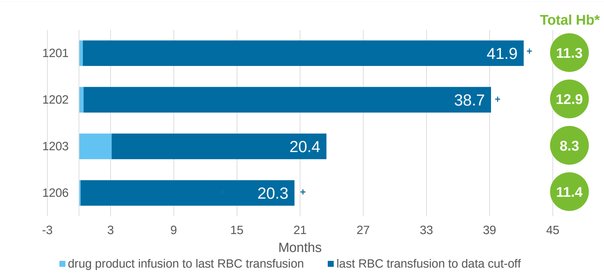
Peripheral VCN



HbA^{T87Q} Production



Freedom from pRBC Transfusion



**Hemoglobin (g/dL) at most recent study visit*

+ Discontinued iron chelation and transitioned to therapeutic phlebotomy: Patients 1201 (started Aug. 2016), 1202 (started Nov. 2015), 1206 (started Oct. 2016)

Safety in Treated Patients

- Adverse events generally consistent with myeloablative conditioning
  - Mucositis (n=2) and elevated AST (n=2) are the only non-hematologic Grade 3-4 AEs in multiple patients
- No drug-product related non-hematologic AEs or SAEs
- Ten SAEs post-LentiGlobin: 1 VOC, 1 ACS, 1 wisdom tooth infection, 1 major depressive disorder, 1 cholestasis, 1 staphylococcus infection, 1 pneumonia infection, 1 case of elevated liver enzymes, and 2 pain episodes (knee pain and rheumatoid pain)
- No replication competent lentivirus (RCL) detected to date
- No evidence of insertional mutagenesis to date

Study Visit	Total unique integration sites
Month 3 (n=3)	1,987 – 3,518
Month 6 (n=5)	719 – 12,631
Month 12 (n=5)	756 – 8,685
Month 24 (n=3)	2,085 – 11,744
Month 30 (n=2)	4290-18,976
Month 36 (n=1)	5585

SUMMARY

- All patients with severe SCD treated with LentiGlobin gene therapy successfully produce therapeutic hemoglobin (HbA^{T87Q})
  - The patient with more than 24 months follow-up (1204) continues to show marked clinical improvement
    - No further evidence of hemolysis
    - Approximately 30 months with no severe SCD-related symptoms, recently 1 VOC following an episode of acute gastroenteritis with fever and dehydration
    - VCN and HbA^{T87Q} in peripheral blood remain stable, with no evidence of decreasing efficacy
  - The more recently treated patients show increasing HbA^{T87Q}
- Patients with TDT with 20 to 42 months of follow-up have been free of chronic transfusions with sustained levels of HbA^{T87Q}
  - Stable total hemoglobin levels >11 g/dL in patients with β0/βE genotypes (n=3)
- Safety profile of LentiGlobin DP in this study continues to appear consistent with autologous transplantation, with no gene-therapy related AEs to date and with continued polyclonal reconstitution

Acknowledgements

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Elisa Magrin has no disclosures to report

**According to treating physician records*

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