Resolution of Sickle Cell Disease Manifestations in Patients Treated with LentiGlobin Gene Therapy: Updated Results from the Phase 1/2 HGB-206 Group C Study

Poster #990

PosterCast

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INTRODUCTION

- Expression of anti-sickling β-globin via gene transfer into hematopoietic stem cells (HSCs) may reduce or eliminate sickle cell disease (SCD) symptoms by reducing HbS levels in red blood cells (RBCs)
- LentiGlobin for SCD gene therapy (GT) comprises autologous CD34+ HSCs transduced with the BB305 lentiviral vector, which encodes human β-globin with an anti-sickling T87Q substitution ($\beta^{A\text{-}T87Q}$)
- The safety and efficacy of LentiGlobin in adults and adolescents with severe SCD is being evaluated in the ongoing multicenter Phase 1/2 study HGB-206 (NCT02140554)
- The first 7 patients (Group A) received drug product (DP) manufactured using bone marrow harvested (BMH) HSCs and demonstrated stable but suboptimal GT-derived hemoglobin (HbA^{T87Q}) expression
- The protocol was amended to include pre-harvest RBC transfusions, higher target busulfan levels and a refined DP manufacturing process to improve HbA^{T87Q} levels (Group B; N = 2)
- An additional modification, collection of HSCs by plerixafor mobilization and apheresis, was introduced in Group C
- Here we present longer follow-up data and data on additional patients in Group C as of the 26 August 2019 data cut date

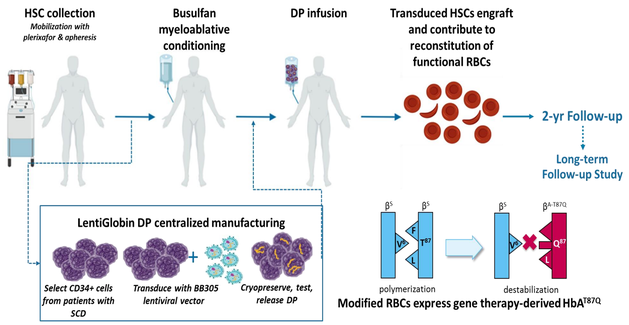
METHODS

- Enrollment criteria for Group C include:
  - ≥ 12 and ≤ 50 years of age
  - History of severe VOEs*
  - Failure or intolerance to hydroxyurea
- Key outcomes for the study are:
  - Weighted average of HbA^{T87Q} ≥ 30% of total Hb for ≥ 6 months following DP infusion
  - Weighted average of total Hb increase ≥ 3 g/dL compared to baseline OR total Hb ≥ 10 g/dL for ≥ 6 months following DP infusion
  - A ≥ 75% reduction in annualized number of severe VOEs in 24 months following DP infusion
- Patients are also monitored for other laboratory and clinical outcomes as well as adverse events (AEs)

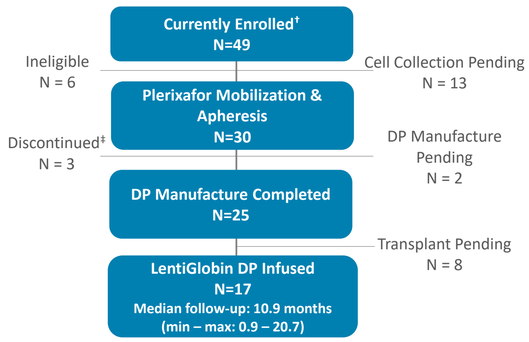
Target enrollment: 41 evaluable subjects †

*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, hepatic sequestration, splenic sequestration, or priapism (priapism episodes considered if medical facility visit was needed). † 6 patients may not meet the severe VOE criteria but will be evaluated for globin response.
DP, drug product; Hb, hemoglobin; VOE, vaso-occlusive event

STUDY DESIGN



STUDY DISPOSITION



†Currently active, not recruiting
‡1 withdrew consent, 1 discontinued due to investigator discretion, 1 mobilization failure

PATIENT CHARACTERISTICS

Table 1. Patient Characteristics for ITT Population

Parameter	N = 30*
Age at consent, years median (min – max)	**25** (12 – 38)
Gender	**12 F 18 M**
Genotype, β^S/β^S	**29**†
SCD history	
VOCs‡, n Annualized no. of events, median (min – max)	**25** **4.0** (2.0 – 15)
ACS¥, n Annualized no. of events, median (min – max)	**2** **1** (1 – 1)
Any history of stroke, n	**6**
TRJV, n	**4**

*30 patients who started cell collection; †1 patient pending; ‡ ≥ 2 events/year in preceding 2 years; ¥ ≥ 2 episodes in preceding 2 years, with ≥ 1 episode in the past year or in the year prior to the initiation of regular transfusions
ACS, acute chest syndrome; F, female; M, male; TRJV, tricuspid regurgitant jet velocity; VOC, vaso-occlusive crisis; ITT=intent to treat

RESULTS

Table 2. Treatment and Drug Product Characteristics

Parameter	N = 17* Median (min – max)
Treatment characteristics	
No. of mobilization cycles	**2** (1 – 4)
CD34+ cells collected per mobilization cycle, $x10^6$ cells/kg	**10.3** (3.9 – 55.4)
Average busulfan AUC, min*μmol/L	**4874** (4307 – 5182)
Follow-up, months	**10.9** (0.9 – 20.7)
Neutrophil engraftment, days (ANC ≥ 500 /μL)	**20** (15 – 26)
Platelet engraftment, days (platelets > 50k /μL)	**28** (17 – 136)
Duration of hospitalization, days	**36** (30 – 65)
Drug product characteristics	
Vector copy number	**3.6** (2.3 – 5.6)
% Transduced cells	**80.2** (63 – 90)
CD34+ cell dose, $x10^6$ cells/kg	**6.3** (3.0 – 14.0)

*17 patients infused
ANC, absolute neutrophil count; AUC, area under the curve

RESULTS

Table 3. Safety Profile Post-LentiGlobin Infusion

Non-hematologic Grade ≥ 3 AEs *Post-DP infusion in ≥ 2 patients**	N = 17 n (%)
Febrile neutropenia	10 (58.8)
Stomatitis	9 (52.9)
Increased blood bilirubin	3 (17.6)
Upper abdominal pain	2 (11.8)
Increased alanine aminotransferase	2 (11.8)
Increased aspartate aminotransferase	2 (11.8)
Nausea	2 (11.8)
Premature menopause	2 (11.8)
Serious AEs *Post-DP infusion in ≥ 2 patients*	**N = 17** n (%)
Nausea	2 (11.8)
Vomiting	2 (11.8)

*Hematologic AEs commonly observed post-transplantation have been excluded
RCL, replication competent lentivirus

- Safety profile post-DP infusion is generally consistent with myeloablative single-agent busulfan conditioning
- No DP-related adverse events
- No cases of veno-occlusive liver disease
- No graft failure or deaths reported
- No vector-mediated RCL
- No evidence of clonal dominance

Figure 1. HbA^{T87Q} and Total Hb Over Time

*Shows number of patients for whom data are available, Median (Q1, Q3) depicted; †Key outcome includes total Hb ≥ 10 g/dL

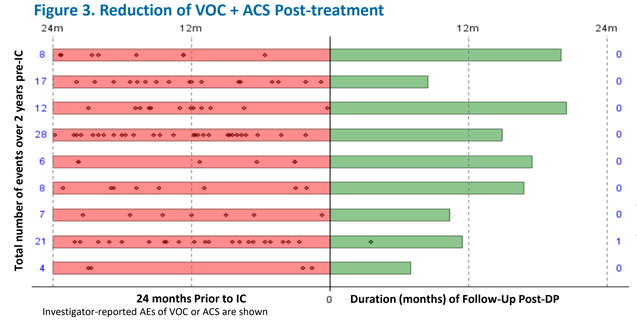
- Median total Hb at screening was 9.3 (6.8 – 12.2) g/dL (includes some patients on chronic transfusions)
- Median total Hb is maintained at 10 g/dL post-LentiGlobin treatment with stable levels of HbA^{T87Q}

Figure 2. Hb Fractions Post-LentiGlobin Treatment

% represents median Hb fraction as % of total Hb

- Median HbS ≤ 60% at ≥ 6 months post-LentiGlobin treatment
- Median anti-sickling HbA^{T87Q} contribution is ≥ 40% at ≥ 6 months
- Total Hb and HbA^{T87Q} ranged from 9.3 – 15.2 g/dL and 2.7 – 9.0 g/dL, respectively, at last visit in patients with ≥ 6 months of follow-up

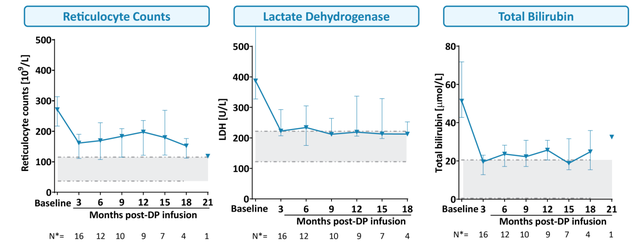
Figure 3. Reduction of VOC + ACS Post-treatment



Investigator-reported AEs of VOC or ACS are shown
*Patients with ≥ 4 VOC/ACS at baseline before IC and with ~ ≥ 6 months of follow-up post-DP infusion are included
IC, informed consent

- The reduction of annualized rate is 99% [95% confidence interval, 92.5 – 100%]
- No ACS or serious VOCs occurred in any Group C patient post-LentiGlobin treatment to date (between 1-21 months follow-up)
- As previously reported, 1 non-serious Grade 2 VOC was observed in 1 patient ~ 3.5 months post-LentiGlobin treatment

Figure 4. Hemolysis Markers Post-LentiGlobin Treatment



Median (Q1, Q3) depicted; Dot-dash lines denote lower and upper limits of normal values
*Number of patients with data available

- Hemolysis markers decreased post-LentiGlobin treatment

SUMMARY

- The safety profile post-LentiGlobin for SCD gene therapy is generally consistent with that of myeloablative single-agent busulfan conditioning
- No ACS or serious VOCs were observed in Group C patients with 1 to 21 months follow-up post-LentiGlobin treatment
- Median HbS levels were ≤ 60% at ≥ 6 months post-LentiGlobin treatment, with a median anti-sickling HbA^{T87Q} contribution ≥ 40%
- Median total unsupported Hb was ≥ 10 g/dL at last visit in patients with ≥ 6 months of follow-up
- Treatment with LentiGlobin decreased key markers of hemolysis
- Longer follow-up for durability and safety in this study, and data from additional studies, will help further assess the clinical impact of LentiGlobin for SCD

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DISCLOSURES

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