Single-Agent Plerixafor Mobilization to Collect Autologous Stem Cells for Use in Gene Therapy for Severe Sickle Cell Disease

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BACKGROUND

- Patients with severe sickle cell disease (SCD) may benefit from β-globin gene transfer into autologous hematopoietic stem cells (HSCs), to enable production of adult hemoglobin (HbA), and prevent red blood cell (RBC) aggregation and correct hemolytic anemia
- LentiGlobin Drug Product (DP) contains autologous CD34+ HSCs transduced with the BB305 lentiviral vector, encoding a human β-globin gene with a single point mutation (T87Q) to confer anti-sickling properties similar to γ-globin
- Proof-of-concept was established in the HGB-205 study: 13 year old patient had 5.7 g/dL HbA^{T87Q} (~50% of total Hb) in blood that correlated with significant clinical improvement[1]
- Phase 1 HGB-206 study was initiated to evaluate the safety and efficacy of LentiGlobin DP in severe SCD
  - Early results in first 7 patients showed low HbA^{T87Q} levels (0.09 – 2.03 g/dL)[2]
- To optimize clinical benefit, the HGB-206 protocol was modified to:
  - Initiate chronic RBC transfusions before HSC collection
  - Increase target busulfan levels to optimize marrow ablation
  - Use a refined manufacturing process to increase vector copy number (VCN) in DP
  - Utilize plerixafor-mobilized HSCs in lieu of bone marrow harvested (BMH) cells (G-CSF is contraindicated in patients with SCD due to life-threatening complications)[3-5]
- We present early results in patients treated under the modified protocol

METHODS

- Phase 1 study of LentiGlobin DP in patients aged ≥18 years with severe SCD (history of recurrent vaso-occlusive crisis [VOC], acute chest syndrome [ACS], stroke, or tricuspid regurgitant jet velocity of >2.5 m/s)
- **Group A** (fully enrolled, n=7 infused): Patients received DP manufactured from **BMH HSCs** under **original** protocol
- **Group B** (fully enrolled, n=2 infused): Patients received DP manufactured from **BMH HSCs** under **modified** protocol
  - During this time, the LentiGlobin manufacturing process was refined to increase proportion of transduced cells
- **Group C** (enrolling, n=1 infused): Patients received DP manufactured from **plerixafor-mobilized HSCs** under **modified** protocol
- Plerixafor mobilization of HSCs into peripheral blood (PB):
  - Patients receive 240 μg/kg plerixafor followed 4 to 6 hours later by apheresis, processing ~3 total blood volumes
  - Patients can undergo up to 2 mobilization cycles, ≥ 2 weeks apart; each cycle can include up to 2 days of apheresis with daily plerixafor
- Patients were monitored for adverse events (AEs), VCN, HbA^{T87Q} production, and clinical and laboratory parameters

STUDY DESCRIPTION

Figure 1. HGB-206: Study design

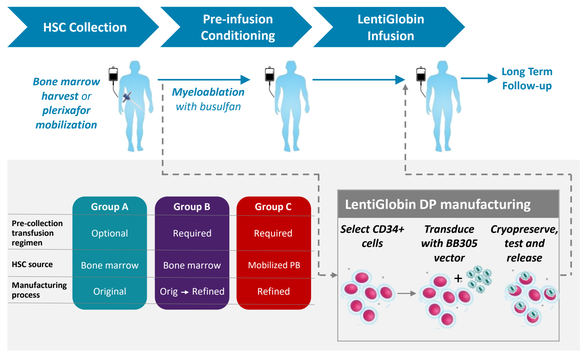
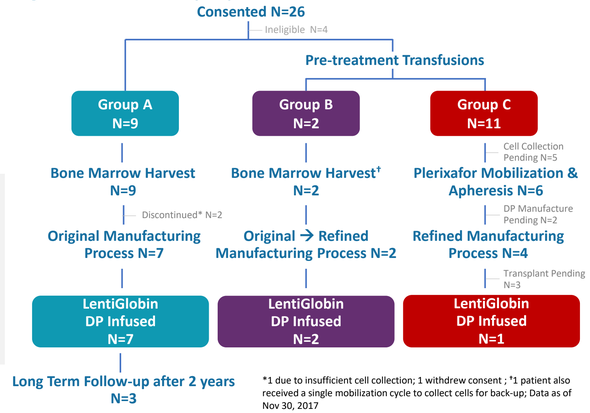


Figure 2. HGB-206: Study disposition



*1 due to insufficient cell collection; 1 withdrew consent ; †1 patient also received a single mobilization cycle to collect cells for back-up; Data as of Nov 30, 2017

Table 1. Patient baseline characteristics
(N=17 patients with cells collected)

Parameter		
Age at enrollment, years; median (min – max)	**26** (18 – 43)	
Gender	**5 Female, 12 Male**	
Genotype, β^S/β^S	**17** (100%)	
Follow-up, months; median (min – max)	**20.9** (0.9 – 26.7)	
Prior SCD History/Complications	**No. of Patients**	**Median (min - max)†**
Hydroxyurea	**11**	NA
Recurrent VOCs*	**14**	4.3 (0.5 – 27.5)
Acute chest syndrome*	**11**	0.5 (0.5 – 1)
Any history of stroke	**3**	NA
Regular pRBC transfusions prior to study entry	**4**	NA
TRJV >2.5 m/s*	**1**	NA

*Within 2 years prior to informed consent; †Median annualized values for VOCs and ACS in patients with the event; TRJV=Tricuspid regurgitant jet velocity; NA=Not applicable; Data as of Nov 30, 2017

RESULTS

Table 2. Treatment characteristics in treated patients

Parameter	Group A N=7 Median (min-max)	Group B N=2 Median (min-max)	Group C† N=1 Median (min-max)
No. of bone marrow harvests	**2** (1 – 4)	**2.5** (2 – 3)	--
No. of mobilization cycles	--	1[4]	**1.5** (1-2)[5]
Busulfan AUC[1], *μM*min*	**4747** (4084 – 5290)	**5017**, NA	**5182**
Neutrophil engraftment, *days*[2]	**22** (17 – 29)	**26** (23 – 28)	**20**
Platelet engraftment, *days*[3]	**56** (29 – 63)	**46** (31 – 61)	NA

[1]Estimated average daily busulfan exposure over 4 days. [2]Absolute neutrophil count [ANC] ≥ 500 cells/μL for 3 consecutive days. [3]Unsupported platelet count ≥ 50,000/μL for 3 consecutive measures. [4]For research purposes. NA = Not available. †Includes data for 5 additional patients who were mobilized but not yet treated; Data as of Oct 26, 2017; †Data as of Nov 30, 2017

Safety associated with cell collection

Table 3. Bone marrow harvest

In 26 BMHs in 9 patients (7 Group A and 2 Group B), 17 grade ≥3 AEs were reported in 5 patients

Grade ≥ 3 AEs in patients who had BMH (N=9)	Patients n (%)
Procedural pain[1]	5 (56)
Anemia	2 (22)
SCD-related pain crises[2]	2 (22)
Decreased lymphocyte count	1 (11)

[1]Considered serious in 1 patient
[2]3 events in 2 patients, all considered serious

Table 4. Mobilization & apheresis

In 10 mobilizations in 7 patients (1 Group B and 6 Group C), 5 grade ≥3 AEs were reported in 3 patients

Grade ≥ 3 AEs in patients who had apheresis (N=7)	Patients n (%)
Hypomagnesimia	1 (14)
Non-cardiac chest pain	1 (14)
SCD-related pain crises[1]	3 (43)

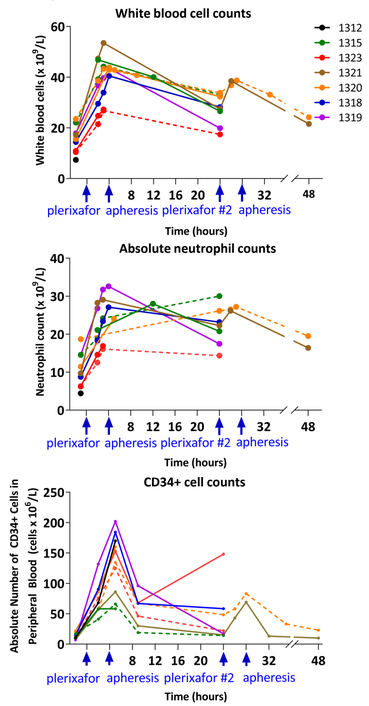
[1]Considered serious; were consistent with patients' histories of vaso-occlusive events. Patients were hospitalized, or hospitalization was prolonged, for standard management. All 3 patients recovered without sequelae.

Safety post-LentiGlobin DP infusion

- Grade ≥3 hematologic AEs consistent with myeloablative busulfan
- Most common grade ≥3 non-hematologic AEs in Group A and B patients were stomatitis (n=7), sickle cell anemia with crisis (n=5, considered serious in 4 patients) and febrile neutropenia (n=5)
- 1 AE (hot flush, grade 1) in Group B considered possibly related to DP
- For 1 DP-infused patient in Group C, no unexpected grade ≥3 AEs, no SAEs or DP-related AEs were reported*
- No replication competent lentivirus detected; continued highly polyclonal repopulation

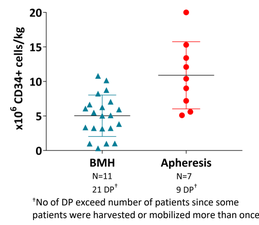
Data as of Oct 26, 2017; *Data as of Nov 30, 2017

Figure 3. PB cell counts after plerixafor dosing, and before and after apheresis



Two patients received a second dose of plerixafor ~24 hours after dose 1, and had a second apheresis, as part of a single mobilization cycle. Three patients underwent a second mobilization cycle, represented by dashed lines.

Figure 4. Total CD34+ cells collected per collection cycle

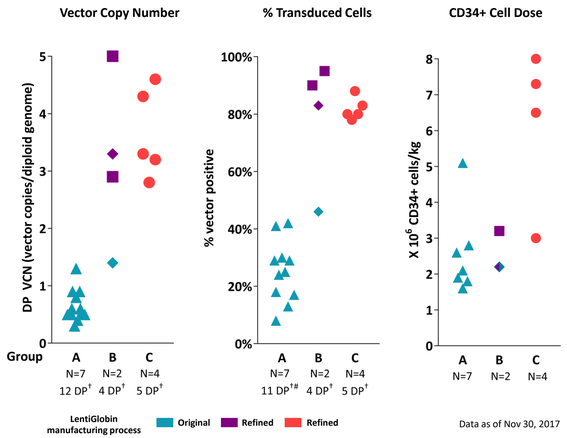


†No of DP exceed number of patients since some patients were harvested or mobilized more than once

A median of 5.0 (0.3 – 10.8) x 10^6 CD34+ cells/kg were collected per BMH. A median of 10.4 (5.1 – 20.0) x 10^6 CD34+ cells/kg were collected per mobilization cycle.

Sufficient cells for both DP manufacture and back-up were collected in 1 mobilization cycle in 3 of 6 Group C patients. A median of 2 (1 – 4) BMH were required to collect adequate cells for both DP manufacture and back-up.

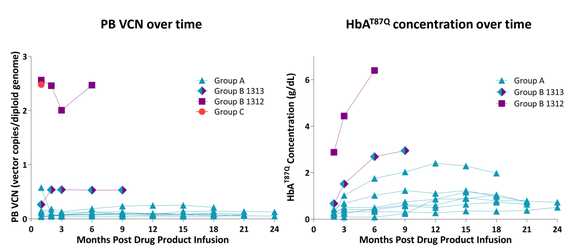
Figure 5. Refinements to manufacturing and cell harvest lead to improved drug product characteristics



Data as of Nov 30, 2017

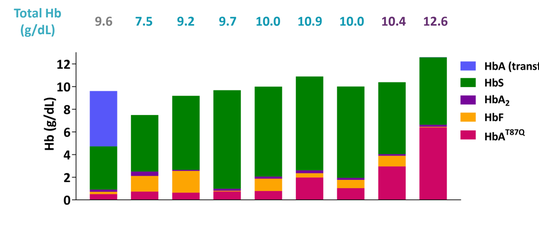
†No of DP exceed number of patients since some patients were harvested or mobilized more than once; #% Transduced cells not available for 1 DP at time of analyses

Figure 6. Patients treated under the modified protocol have higher PB VCN and HbA^{T87Q} levels



Data as of: Oct 26, 2017 (Grp A); Nov 30, 2017 (Grp B); Dec 6, 2017 (Grp C)

Figure 7. Higher vector-derived Hb in patients treated under modified protocol and refined manufacturing process



	1301	1303	1304	1306	1308	1309	1310	1313	1312*
Follow up (months)	24	24	21	21	21	18	18	9	6
% HbA^{T87Q}	5	10	7	8	8	18	10	28	51
% HbF	2	18	21	1	11	3	7	9	0
% HbS	40	67	71	90	79	76	81	61	47

Data as of Oct 26, 2017; *Data as of Nov 30, 2017

SUMMARY

- Early data with modified protocol and refined manufacturing process demonstrate:
  - Higher PB VCNs than observed in prior treated patients
  - HbA^{T87Q} levels as high as 6.4 g/dL (51% of total Hb) at 6 months in one patient
- Engraftment and safety profile consistent with previous findings
- Use of single-agent plerixafor mobilization and apheresis for LentiGlobin DP manufacture in patients with severe SCD is feasible:
  - Acceptable safety profile to date, VOCs observed were milder in severity than reported with G-CSF and resolved without sequelae
  - Fewer grade ≥3 AEs per patient were reported with mobilization and apheresis than with BMH
  - Median amount of CD34+ cells collected in a single mobilization cycle was more than double that collected in a single BMH
  - Similar gene therapy vector transduction efficiency in HSCs obtained via BMH and mobilization
- Future results from patients treated in Group C will determine the collective effects of all protocol and process changes

REFERENCES

1. Ribeil et al. *N Eng J Med*. 2017; 2. Kanter et al., Oral presentation at ASH 2016; Abstract #1176; 3. Adler et al. *Blood*. 2001; 4. Abboud et al., *Lancet*. 1998; 5. Wei et al., *Blood*. 2001

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DISCLOSURES

Dr. Tisdale has no conflicts of interest to report.

ASBMT 2018 Abstract 188