Betibeglogene autotemcel (LentiGlobin for β-thalassemia) in patients with transfusion-dependent β-thalassemia and β^0/β^0, β^+ IVS1-110/β^+ IVS1-110, or β^0/β^+ IVS1-110 genotypes: updated results from the HGB-212 study

Poster EP1494

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BACKGROUND

- Gene therapy with betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) is a one-time treatment option for patients with transfusion-dependent β-thalassemia (TDT).
- Beti-cel adds functional copies of a modified *HBB* gene into patients' hematopoietic stem cells (HSC) through transduction of autologous CD34+ cells with BB305 lentiviral vector, thereby addressing the underlying genetic cause of TDT.
- Patients with TDT who have a β^0/β^0 genotype are unable to produce any β-globin while the β^+ IVS-I-110 (G>A) mutation results in minimal endogenous β-globin expression[1]
- In the phase 1/2 HGB-204 study, the majority of patients with non-β^0/β^0 genotypes became transfusion independent (TI) while transfusion requirements were reduced in the majority of patients with β^0/β^0 genotypes with 3/8 patients achieving TI[2]
- The phase 3 HGB-212 study (NCT03207009) is evaluating the outcomes of patients with β^0/β^0, β^+ IVS1-110/β^+ IVS1-110, or β^0/β^+ IVS1-110 genotypes treated with beti-cel manufactured under refined conditions compared to HGB-204 with the goal of improving clinical outcomes.

METHODS & STUDY DESIGN

Key eligibility criteria

- TDT: ≥ 100 mL/kg/yr of packed red blood cells (pRBC) or ≥ 8 pRBC transfusions/yr
- β^0/β^0, β^+ IVS1-110/β^+ IVS1-110, β^0/β^+ IVS1-110 genotype
- ≤ 50 years of age

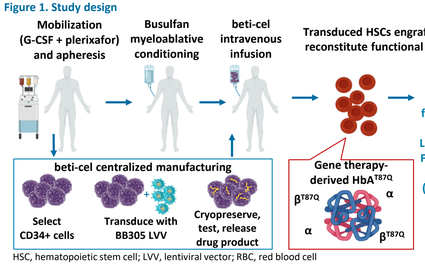
Primary endpoint: Transfusion reduction

- ≥ 60% reduction in pRBC transfusion volume between Month 12 – 24

Key secondary endpoint: Transfusion independence (TI)

- Weighted average hemoglobin (Hb) ≥ 9 g/dL without pRBC transfusions for ≥ 12 months

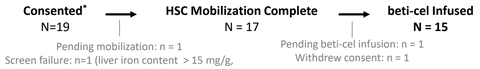
Figure 1. Study design



HSC, hematopoietic stem cell; LVV, lentiviral vector; RBC, red blood cell

STUDY DISPOSITION

Figure 2. HGB-212 enrollment



- **Median follow-up: 14.4 months** (min – max: 1.1 – 24.0 months)
- One patient with sufficient follow-up has enrolled in LTF-303 (NCT02633943)
- Target enrollment: N=18 patients
- Interim datacut: Last patient visit: 3 March 2020; Database lock 7 April 2020

RESULTS

Table 1. Patient characteristics

		N = 15 median (min – max)
***HBB* Genotype,** n (%)	β^0/β^0	**9** (60)
	β^+ IVS1-110/β^+ IVS1-110	**3** (20)
	β^0/β^+ IVS1-110	**3** (20)
Age, years	First pRBC transfusion	**0.7** (0.3 – 11.0)
	Start of iron chelation	**3.0** (0.7 – 11.0)
	Consent for HGB-212	**15** (4 – 33)
Male, n (%)		**8** (53)
Liver iron concentration, mg Fe/g dw		**5.8** (1.2 – 13.2)
Cardiac T2*, msec		**39** (15 – 75)
Splenectomy, n (%)		**3** (20)
Annualized† pre-study pRBC transfusions	Transfusion volume, mL/kg/yr	**181** (75 – 276)
	Number of transfusions, n/yr	**17.5** (11.0 – 39.5)
	Pre-transfusion Hb, g/dL	**9.5** (8.2 – 10.7)

†Retrospective data 2 years prior to study enrollment. Hb, hemoglobin; pRBC, packed red blood cell

RESULTS

Mobilization and drug product characteristics

- Target cell dose for collection: ≥12.0 × 10^6 CD34+ cells/kg
  - Minimum for rescue: ≥1.5 × 10^6 CD34+ cells/kg
  - Minimum beti-cel dose for infusion: ≥5.0 × 10^6 CD34+ cells/kg
- The majority of patients (73%; 11/15) required one mobilization cycle
  - Three patients needed 2 cycles; one patient required 3 cycles

Table 2. Drug product characteristics (per patient)

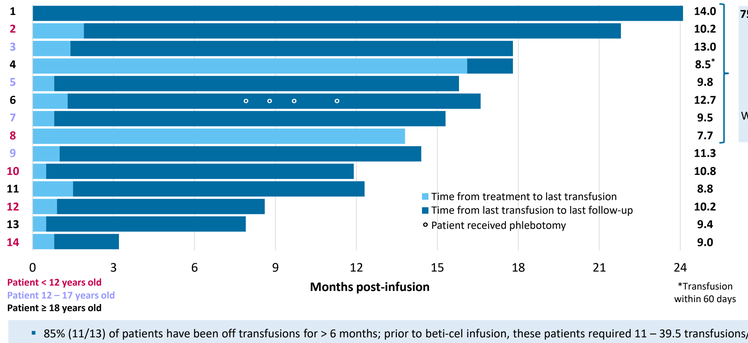
	N = 15 median (min – max)
Vector copy number, vector copies/diploid genome	**2.5** (1.2 – 6.0)
CD34+ cells transduced, %	**73** (34 – 90)
Cell dose, x 10^6 CD34+ cells/kg	**11.1** (5.9 – 15.8)

Table 3. Conditioning and Engraftment

	N=15* median (min – max)
Conditioning	
Daily average estimated busulfan AUC over 4 days, μM*min	**4372** (3824 – 9086)
Engraftment	
ANC ≥ 500 cells/μL x 3 days	**26** (14 – 38)
Platelets ≥ 20,000 cells/μL x 3 days	**41** (21 – 64)

ANC, absolute neutrophil count; AUC, area under the curve; *Two patients with 1 and 3 months follow-up had not yet achieved platelet engraftment as of the datacut

Figure 3. Transfusion status after beti-cel gene therapy in patients with ≥ 3 months follow-up



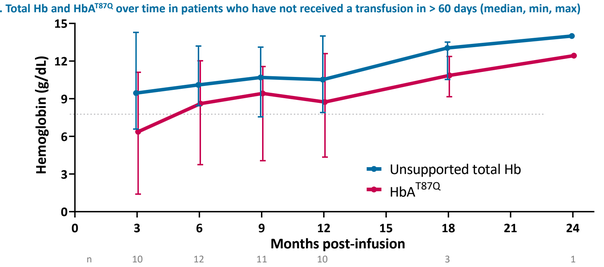
75% (6/8) of evaluable patients achieved transfusion independence (TI)

Median duration of TI: 13.6 (12.2 – 21.2) months

Weighted average Hb during TI: 11.5 (9.5 – 13.5) g/dL

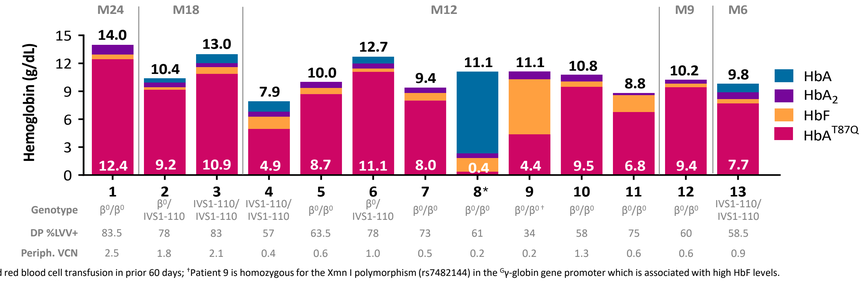
- 85% (11/13) of patients have been off transfusions for > 6 months; prior to beti-cel infusion, these patients required 11 – 39.5 transfusions/year
- Patient 4 and Patient 8 continue to receive pRBC transfusions and had an 80% and 31% reduction in number of transfusions, respectively

Figure 4. Total Hb and HbA^{T87Q} over time in patients who have not received a transfusion in > 60 days (median, min, max)



- As transduced HSCs engraft and produce mature RBCs, HbA^{T87Q} levels increase and stabilize in individual patients ~6 – 9 months after beti-cel infusion

Figure 5. Hemoglobin fractions at last visit in patients with > 6 months follow-up



*Packed red blood cell transfusion in prior 60 days; †Patient 9 is homozygous for the Xmn I polymorphism (rs7482144) in the $^G\gamma$-globin gene promoter which is associated with high HbF levels.
DP, drug product, VCN, vector copy number

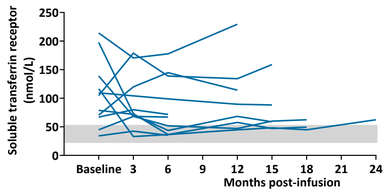
- HbA^{T87Q} contributes to the majority of total Hb (62 – 92%) in 11/13 patients

Figure 6. Assessment of erythropoiesis biomarkers in patients who have been transfusion free for > 6 months (n=11); Gray indicates normal range

- Erythropoietin decreased from baseline to Month 12 in 6/7 transfusion-free patients*
  - Baseline min – max: 8.9 – 258.5 U/L; Month 12 min – max: 8.6 – 149.9 U/L

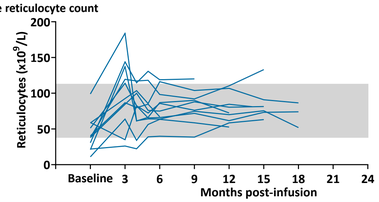
*Baseline and Month 12 values not available for 4 patients

A. Soluble Transferrin Receptor (sTfR)



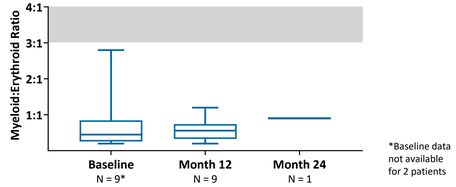
- At baseline, the majority (9/11) of patients showed elevated levels of sTfR (min – max: 34 – 214 nmol/L in all 11 patients) which has been associated with increased erythropoiesis[3]
- There was a decrease in sTfR from baseline to Month 12 in 5/8 patients
  - At Month 12, the change in sTfR from baseline ranged from -71% to +62% (n=8)

B. Absolute reticulocyte count



- Reticulocytes in the blood were generally within the normal range after beti-cel infusion

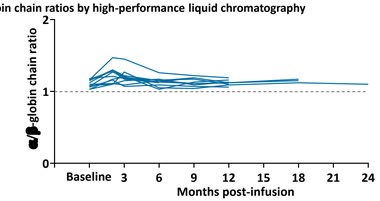
C. Myeloid:Erythroid ratio



*Baseline data not available for 2 patients

- Myeloid:erythroid ratio was generally stable between baseline and Month 12, but did increase by 6% to 471% in 5/8 patients between baseline and Month 12

D. α/β-globin chain ratios by high-performance liquid chromatography



- At baseline, patients had α/β-globin ratios that were close to 1.00 (1.03 – 1.18) due to the contribution from transfused blood, as expected[4-7]
- In the absence of transfusions post-beti-cel, patients achieve and maintain near-normal α/β- ratios

Safety profile following beti-cel infusion

Table 4. Adverse events (AE) after beti-cel infusion

Non-hematologic grade ≥ 3 AEs* *Infusion to 2-year follow-up in ≥ 2 patients*	**N = 15 n (%)**
Febrile neutropenia	9 (60)
Stomatitis	5 (33)
Alanine aminotransferase increased	3 (20)
Decreased appetite	3 (20)
Mucosal inflammation	3 (20)
Pharyngeal inflammation	2 (13)
AEs considered possibly related to beti-cel† *Post-infusion in ≥ 1 patient*	
Abdominal pain	2 (13)
Leukopenia	1 (7)
Neutropenia	1 (7)
Thrombocytopenia	1 (7)

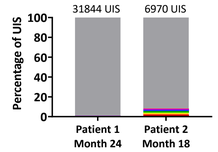
*Hematologic AEs commonly observed post-transplantation have been excluded. †As assessed by the investigator

- All AEs attributed to beti-cel were grade 1/2
- 8 serious AEs post-infusion in 3 patients, all events resolved:
  - Pyrexia (n=2); congestive cardiac failure (CHF), febrile neutropenia, headache, neutropenia, stomatitis, and thrombocytopenia (all n=1)
    - The serious, grade 3 CHF event was considered likely related to baseline cardiac iron overload (baseline cardiac T2* 16.6 msec) and conditioning by the investigator
      - CHF was diagnosed 18 days after beti-cel infusion (LVEF was 21%)
      - Following treatment and chelation, patient was asymptomatic after ~4 months, LVEF was 53% and cardiac T2* was 13 msec
      - The event resolved one year after beti-cel infusion
- No cases of veno-occlusive disease (VOD); 14/15 patients received VOD prophylaxis
- No graft failure, deaths, replication-competent lentivirus or insertional oncogenesis

Integration site analysis (ISA) in transduced peripheral blood mononuclear cells

- There has been no clonal dominance observed
- At Month 12, the highest percentage of unique integration sites (UIS) per patient (n=9) ranged from 0.1% to 4.2% and total number ranged from 2758 to 19392 UIS

Figure 7. Top ten most frequent integration sites in patients with ≥ Month 18 evaluation



- In patients with ≥ Month 18 ISA evaluation (n=2), the top 10 most frequent integration sites are indicated by a different color in Figure 7, with gray indicating the cumulative proportion of all the other integration sites
- The most frequent integration detected in each patient at last evaluation was 0.2% (Patient 1) and 1.2% (Patient 2) indicating highly polyclonal reconstitution by vector-positive HSCs

SUMMARY

- HGB-212 (Northstar-3) is a single-arm, international, phase 3 study evaluating the safety and efficacy of betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy in patients with TDT who have a β^0/β^0, β^0/β^+IVS-I-110 or β^+IVS-I-110/β^+IVS-I-110 genotype.
- 85% (11/13) of patients have been able to stop pRBC transfusions for > 6 months, including one patient with 61% endogenous Hb (HbF + HbA$_2$)
- Gene therapy-derived HbA^{T87Q} was high enough to support Hb > 9 g/dL in 10/11 patients who stopped transfusions for > 6 months
- 75% (6/8) of evaluable patients achieved transfusion independence
  - Median weighted average Hb during TI was 11.5 (9.5 – 13.4) g/dL
- A trend towards improvement in erythropoiesis was seen in patients who stopped transfusions
- Hematopoietic reconstitution is polyclonal and there is no evidence of clonal dominance or insertional oncogenesis
- The treatment regimen comprising conditioning and beti-cel infusion had a tolerability profile dominated by the known effects of myeloablation with single agent busulfan

ACKNOWLEDGMENTS

We thank all the patient participants and their families. We thank all the HGB-212 study sites, Manfred Schmidt of GeneWerk, GmbH for integration site analyses, and the study sponsor bluebird bio. Editorial assistance for this poster was provided by Kimberly Price, PharmD of bluebird bio.

DISCLOSURES

Dr. Yannaki: Research funding by bluebird bio, Gilead, Novartis, Sandoz

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