Long Term Outcomes of 63 Patients with Transfusion-Dependent β-Thalassemia (TDT) Followed Up to 8 Years Post-Treatment with betibeglogene autotemcel (beti-cel) Gene Therapy and Exploratory Analysis of Predictors of Successful Treatment Outcomes in Phase 3 Trials

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INTRODUCTION

- beti-cel is a US Food and Drug Administration approved gene therapy (GT) indicated for adult and pediatric patients with β-thalassemia, who require regular red blood cell transfusions, regardless of age or genotype.[1,2]
- beti-cel treatment addresses the underlying cause of transfusion-dependent β-thalassemia (TDT) by adding functional copies of a modified *HBB* gene, $\beta^{A\text{-}T87Q}$, to autologous CD34+ hematopoietic stem cells (HSCs) through transduction with BB305 lentiviral vector (LVV).[3]
- We previously showed durable transfusion independence (TI), improvement in markers of ineffective erythropoiesis and iron overload, and a favorable risk-benefit profile in patients treated with beti-cel.[4]
- Here, we report up to 8 years of efficacy and safety follow up across phase 1/2, phase 3, and long-term follow-up (LTF) studies of patients treated with beti-cel.
  - All patients are TI evaluable in the phase 3 studies.
- An exploratory analysis of predictors of successful treatment outcomes in patients from the phase 3 studies is also presented.[5]

METHODS

- Patients with TDT underwent HSC collection after mobilization with granulocyte colony-stimulating factor and plerixafor, followed by pharmacokinetic-adjusted myeloablative busulfan conditioning and beti-cel infusion.
- Patients were followed for 2 years in the parent phase 1/2 (HGB-204, NCT01745120; HGB-205, NCT02151526) and phase 3 (HGB-207, NCT02906202; HGB-212, NCT03207009) studies.
  - Enrollment and all beti-cel infusions have been completed.
- Patients then entered a 13-yr LTF study, LTF-303 (NCT02633943).
- The primary efficacy outcome, TI, was defined as weighted average hemoglobin (Hb) ≥9 g/dL without packed red blood cell transfusions for ≥12 months.
- A post-hoc exploratory multivariate analysis was also carried out in patients enrolled in the phase 3 studies to identify predictors of clinical efficacy (TI).
  - 27 variables related to patient medical history (age, disease genotype, splenectomy, extramedullary disease, and treatment site), and manufacturing parameters and drug product attributes (multiplicity of infection, manufacturing site, cell processing steps, transduction efficiency [vector copy number (VCN) and %LVV+ cells], dose size, colony-forming ability, and drug product cell type composition) were analyzed.

RESULTS

Baseline characteristics

- As of July 2022, 63 patients who received beti-cel infusion have been followed for a median (min–max) of 52.0 (20.1–101.7) months across the 4 parent studies and LTF (**Table 1**).

Table 1. Baseline patient characteristics.

Instrument	Phase 1/2 (N=22)	Phase 3 (N=41)
Genotype, n (%)		
non-β^0/β^0	14 (64)	29 (71)
β^0/β^0	8 (36)	12 (29)
Age at consent, median (min–max), years	20 (12–35)	13 (4–34)
Liver iron concentration, median (min–max), mg Fe/g dw	7.1 (0.4–26.4)	4.9 (1.0–41.0)
Cardiac T2*, median (min–max), msec	34 (10–54)	37 (15–75)
Splenectomy, n (%)	9 (41)	7 (17)
Fertility preservation[a], n (%)	13 (59)	30 (73)
Follow-up, median (min–max)	85.0 (67.9–101.7)	42.4 (20.1–64.6)

[a]Fertility preservation was an optional procedure.
Fe/g dw, iron content per gram dry weight.

Hematopoietic recovery after beti-cel infusion

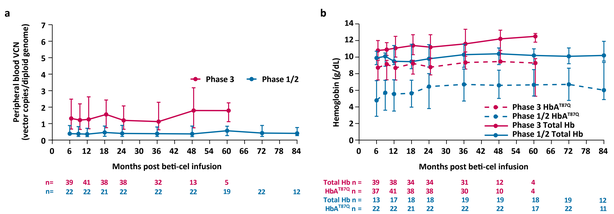
- The median time (min–max) to neutrophil and platelet engraftment was 23 (13–39) and 45 (19–191) days, respectively.
- Lymphocyte subsets were generally within normal range after beti-cel infusion (data as of August 2021).

RESULTS (CONTINUED)

Drug product characteristics

- Peripheral blood VCN, levels of GT–derived adult Hb (HbA^{T87Q}), and total Hb were stable and durable across studies and higher in phase 3 vs phase 1/2 studies following optimized beti-cel drug product manufacturing (**Figure 1**).
- HbA^{T87Q} levels stabilized by Month 6 and contributed to stable levels of total Hb.
- Total unsupported Hb levels ≥9 g/dL at Month 6 were significantly associated with achieving TI ($P<0.0001$) (March 2021 data cut).

Figure 1. (a) Median peripheral blood VCN following beti-cel treatment. (b) Total unsupported Hb and gene therapy-derived HbA^{T87Q}.

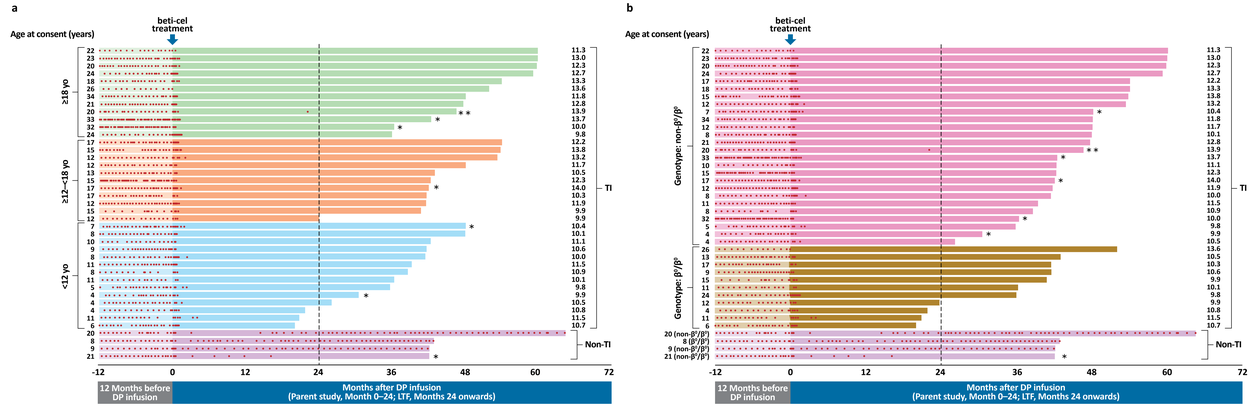


Median (Q1, Q3) depicted.
Hb, hemoglobin; VCN, vector copy number.

Achievement and maintenance of TI

- 52 patients achieved TI: 15/22 (68.2%) in phase 1/2 and 37/41 (90.2%) in phase 3.
- Manufacturing process was refined between phase 1/2 and phase 3; beti-cel approval is based on the drug product used in phase 3 study.
- One-time beti-cel GT in phase 3 studies was followed by durable TI with a median follow up of 42.4 months (**Figure 2**).
  - The results are consistent across ages and genotypes.
- Two patients required packed red blood cell (pRBC) transfusions for acute events (for surgery, phase 3, n=1; for bloody diarrhea and influenza infection, phase 1/2, n=1 [late breaking data])
  - Both patients continue to benefit from treatment and do not require chronic pRBC transfusions to manage β-thalassemia.

Figure 2. Transfusion status in phase 3 patients according to (a) age and (b) genotype.

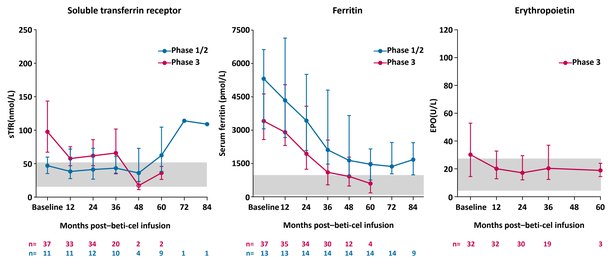


*Indicates 6 IVS-1-110 homozygous or IVS-1-110/β^0 genotype. **After a planned orthopedic surgery, the patient had blood loss, which required 1 packed red blood cell transfusion. Numbers at the ends of lanes represent unsupported total Hb (g/dL) at last follow-up. Red dots depict transfusion episodes. Vertical dashed black line denotes completion of parent study and rollover to LTF-303. Data as of July 2022. TI defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months.
DP, drug product; Hb, hemoglobin; TI, transfusion independence; yo, years old

RESULTS (CONTINUED)

- Patients who achieved TI had reductions in markers of ineffective erythropoiesis and iron overload (**Figure 3**).
  - 35/51 (68.6%) of patients (25/37 patients, 67.6% for Phase 3; 10/13 patients, 76.9% for Phase 1/2) who achieved TI stopped iron chelation for at least 6 months post beti-cel infusion.
  - Among patients achieving TI who stopped chelation, 10/25 (28.6%) used phlebotomy.

Figure 3. Improvement in markers of iron overload and ineffective erythropoiesis after beti-cel infusion.



Adverse events

- 19% (12/63) of patients experienced ≥1 adverse event (AE) considered related or possibly related to beti-cel by the investigator.
- The most common beti-cel-related AEs were abdominal pain (5/63 [8%]) and thrombocytopenia (3/63 [5%]) (**Table 2**).
- Veno-occlusive liver disease (serious and nonserious) was reported in 11% (7/63) of patients and resolved after appropriate treatment.
- No malignancies, insertional oncogenesis, vector-derived replication competent lentivirus, or clonal predominance was observed.

RESULTS (CONTINUED)

Table 2. AEs in ≥2 patients.

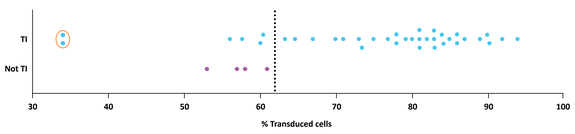
	N=63 n (%)
AEs considered possibly related or related to beti-cel[a]	
Abdominal pain	5 (8)
Thrombocytopenia	3 (5)
Serious AEs	
VOD	5 (8)
Pyrexia	5 (8)
Neutropenia	3 (5)
Thrombocytopenia	3 (5)
Sepsis[b]	3 (5)
Appendicitis	2 (3)
Febrile neutropenia	2 (3)
Major depression	2 (3)
Stomatitis	2 (3)

Data as of July 2022. [a]The following AEs assessed as possibly related or related to beti-cel by the investigator occurred in 1 patient (1.6%): immune thrombocytopenia, leukopenia, neutropenia, tachycardia, dysplasia, non-cardiac chest pain, pain in extremity, focal nodular hyperplasia, dyspnea, and hot flush. [b]Sepsis events included neutropenic sepsis, bacterial sepsis and sepsis not otherwise specified.
AE, adverse event. VOD, veno-occlusive liver disease.

Post-hoc multivariate analysis assessing predictors of clinical outcomes

- An exploratory multivariate analysis in patients from phase 3 studies (n=37; August 2021 data cut) identified that the percentage of cells transduced in the DP with the BB305 LVV (%LVV+ cells; a DP release criteria) was the best predictor of clinical outcomes (**Figure 4**).
- In this retrospective analysis, meeting a threshold of 62% transduced cells increased the likelihood of achieving TI.
- Two patients who achieved TI despite having <40% transduced cells (see orange circle on **Figure 4**) had relatively high endogenous Hb levels.
- Limitations of this study include that this was a post hoc analysis conducted using data from patients who were eligible for beti-cel clinical trials and therefore transplant.

Figure 4. Patients in phase 3 who achieved TI had higher % transduced cells in drug product.



TI, transfusion independence (defined as weighted average hemoglobin ≥9 g/dL without packed red blood cell transfusions for ≥12 months).

CONCLUSIONS

- beti-cel is a potentially curative GT for patients with TDT across ages and genotypes through the achievement of TI and normal or near normal Hb levels.
- Patients with TDT experienced durable TI through up to 8 years following beti-cel infusion, which was associated with a favorable safety profile consistent with that of myeloablative autologous transplantation.
- An exploratory multivariate analysis demonstrated that beti-cel transduction efficiency, as determined by % LVV+ cells, was the most predictive marker for achieving TI.

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