Sustained Efficacy and Safety in Adult and Pediatric Patients With Transfusion-Dependent β-Thalassemia Up to 9 Years Post Treatment With Betibeglogene Autotemcel (Beti-cel)

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INTRODUCTION

- Betibeglogene autotemcel (beti-cel) is a gene therapy approved by the U.S. Food and Drug Administration indicated for adult and pediatric patients with transfusion-dependent β-thalassemia (TDT)[1]
- Beti-cel gene therapy addresses the underlying cause of TDT by adding functional copies of a modified version of the β-globin gene to autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) via a third-generation, self-inactivating lentiviral vector (LVV), BB305[2]
- Following one-time beti-cel therapy, HbA^{T87Q}, normal adult hemoglobin (Hb) containing an amino acid substitution (T→Q) at position 87, is produced in red blood cells (RBCs).[2] HbA^{T87Q} has similar oxygen binding affinity to HbA[3]
- Durable transfusion independence (TI) in patients with TDT, improvements in health-related quality of life (HRQOL), and a favorable risk/benefit profile have been previously reported with beti-cel treatment[4-6]

OBJECTIVE

- To report efficacy, safety, and HRQOL data from adult and pediatric patients treated with beti-cel who were followed for up to 9 years after treatment

METHODS

- Patients with TDT underwent HSPC collection after mobilization with granulocyte colony-stimulating factor and plerixafor, followed by pharmacokinetic-adjusted myeloablative busulfan conditioning and beti-cel infusion[2,6,7]
- Patients who completed either a phase 1/2 (HGB-204 [NCT01745120]; HGB-205 [NCT02151526]) or phase 3 (HGB-207 [NCT02906202]; HGB-212 [NCT03207009]) beti-cel parent study and subsequently participated in the long-term, 13-year follow-up LTF-303 study (NCT02633943) were included in these analyses

Efficacy and safety

- Analyses were conducted by age subgroup according to patient age at enrollment (adult: ≥18 years, adolescent: ≥12 to <18 years, and pediatric: <12 years) to examine:
  - Achievement and maintenance of TI (defined as a weighted average Hb ≥9 g/dL without packed RBC transfusions for ≥12 months)
  - Transduction efficiency and HbA^{T87Q} expression
  - Safety outcomes
- HRQOL was assessed at baseline and every 6 months using the outcome measures shown in **Table 1**
- Data are reported through month 36 for patients in the HGB-204, HGB-207, and HGB-212 studies who had baseline and posttreatment HRQOL scores

Table 1. HRQOL scales[a-11]

Instrument[a]	Population normative mean score	MCID	Ages for which instrument was used in current analyses, y
SF-36	50	2	≥18
FACT-G	80.1	Not established	
FACT-BMT	Not established	Not established	
EQ-5D-3L	Not established	Not established	
PedsQL	82.9	4.4	<18
EQ-5D-Y	Not established	Not established	

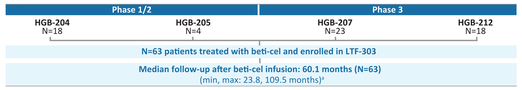
[a]Higher scores indicate better HRQOL.
EQ-5D-3L, EuroQol 5 Dimensions 3 Levels questionnaire; EQ-5D-Y, EuroQol 5 Dimensions Youth questionnaire; FACT-BMT, Functional Assessment of Cancer Therapy-Bone Marrow Transplantation; FACT-G, FACT-General; HRQOL, health-related quality of life; MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SF-36, 36-Item Short Form Health Survey.

RESULTS

Baseline characteristics and follow-up

- As of January 30, 2023, 63 patients had received beti-cel in a phase 1/2 or 3 study and enrolled in LTF-303 (**Figure 1; Table 2**)

Figure 1. Pooled analysis population



[a]Median follow-up for phase 3 patients (n=41): 48.3 months (min, max: 23.8, 71.9 months).

Table 2. Baseline characteristics for patients treated in beti-cel studies

	Phase 1/2 (N=22)	Phase 3 (N=41)
Gender, n (%)		
Male	7 (31.8)	21 (51.2)
Female	15 (68.2)	20 (48.8)
Genotype, n (%)		
Non-β^0/β^{0a}	14 (63.6)	29 (70.7)
β^0/β^0	8 (36.4)	12 (29.3)
Age at enrollment, median (min, max), y	20 (12, 35)	13 (4, 34)
Adult, ≥18 y, n (%)	17 (77.3)	14 (34.1)
Adolescent, ≥12 to <18 y, n (%)	5 (22.7)	11 (26.8)
Pediatric, <12 y, n (%)	0	16 (39.0)
Fertility preservation, n (%)[b]	13 (59.1)	30 (73.2)

[a]Includes non-β^0/β^0 patients phenotypically similar to β^0/β^0 (IVS-1-110 homozygous or IVS-1-110/β^0 genotype). [b]Fertility preservation was an optional procedure.

Transduction efficiency and pharmacodynamic endpoints

- Approximately 80% of phase 3 adolescent and pediatric patients and 64% of adult patients who received beti-cel required only 1 mobilization cycle to achieve the drug product (DP) dose (**Table 3**)
- The median percentage of DP cells transduced with the BB305 LVV, peripheral blood (PB) vector copy number (VCN), and HbA^{T87Q} were comparable across age subgroups

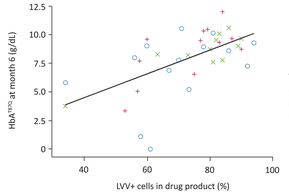
Table 3. Transduction efficiency and pharmacodynamic endpoints by age (phase 3 patients)

	Adult, ≥18 y (n=14)	Adolescent, ≥12 to <18 y (n=11)	Pediatric, <12 y (n=16)
Number of mobilization cycles, n (%)			
1 cycle	9 (64.3)	9 (81.8)	14 (87.5)
2 cycles	5 (35.7)[a]	2 (18.2)	2 (12.5)
DP cells transduced, median (min, max), %	77.5 (53, 90)	82.0 (34, 90)	72.2 (34, 94)
Month 6 PB VCN, median (min, max), c/dg	1.4 (0.2, 3.4)	1.9 (0.2, 4.5)	0.8 (0.2, 3.3)[b]
Month 6 HbA^{T87Q}, median (min, max), g/dL	9.4 (3.4, 12.0)[b]	8.7 (3.8, 10.6)	8.0 (5.2, 10.5)[b]

[a]One patient needed 3 mobilization cycles, but cells from only 2 of these cycles were used for DP manufacturing. [b]n=12.
c/dg, copies/diploid genome; DP, drug product; PB, peripheral blood; VCN, vector copy number.

- Overall, HbA^{T87Q} expression at month 6 was significantly correlated with the proportion of infused LVV+ cells in the DP in the phase 3 studies (**Figure 2**)

Figure 2. HbA^{T87Q} expression at month 6 vs the proportion of LVV+ cells in the DP (phase 3 studies)



DP, drug product; LVV, lentiviral vector.

Achievement and maintenance of transfusion independence

Phase 3 studies

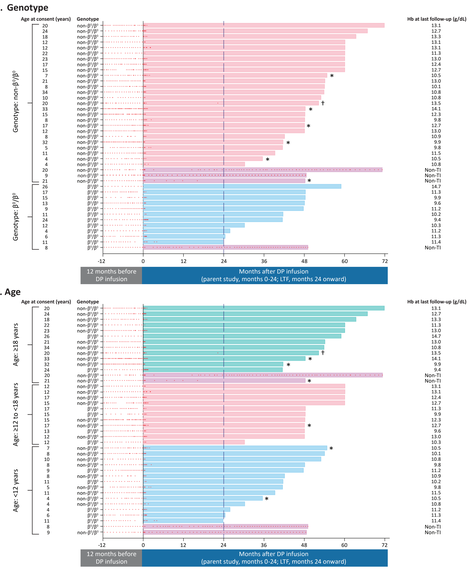
- In the phase 3 studies, in which the commercial DP manufacturing process was used, 90.2% (37/41) of patients achieved and maintained TI through last follow-up (up to 6 years); TI rate and median weighted average Hb were generally similar across study, genotype, and age subgroups (**Table 4; Figure 3**)

Table 4. Proportion of phase 3 patients who achieved TI with beti-cel and total Hb by study, genotype, and age

	N	TI evaluable, n	TI rate, n/N (%)	Weighted average Hb during TI, median (min, max), g/dL
By study				
Phase 3 patients	41	41	**37/41 (90.2)**	11.03 (9.6, 13.7)
HGB-207	23	23	**21/23 (91.3)**	12.06 (9.8, 13.0)
HGB-212	18	18	**16/18 (88.9)**	10.47 (9.6, 13.7)
By genotype				
Non-β^0/β^0	29	29	**26/29 (89.7)**	11.92 (9.8, 13.4)
β^0/β^0	12	12	**11/12 (91.7)**	10.54 (9.6, 13.7)
By age				
Adult, ≥18 y	14	14	**12/14 (85.7)**	12.65 (9.6, 13.7)
Adolescent, ≥12 to <18 y	11	11	**11/11 (100)**	11.80 (10.0, 13.4)
Pediatric, <12 y	16	16	**14/16 (87.5)**	10.41 (9.8, 11.4)

Hb, hemoglobin; TI, transfusion independence.

Figure 3. Transfusion status by (A) genotype and (B) age (phase 3 studies)



Numbers at the ends of lanes represent unsupported total Hb (g/dL) at last follow-up. Red dots depict transfusion episodes. Vertical dashed line denotes completion of parent study and rollover to LTF-303. There were 15 patients with HbE/β^0 genotype enrolled in all studies; 6 were enrolled in phase 3 studies, and all 15 achieved TI.
*Indicates non-β^0/β^0 patients (n=6) phenotypically similar to β^0/β^0 (IVS-1-110 homozygous or IVS-1-110/β^0 genotype). †After a planned orthopedic surgery, the patient had blood loss, which required 1 pRBC transfusion.
DP, drug product; Hb, hemoglobin; LTF, long-term follow-up; pRBC, packed red blood cell; TI, transfusion independent.

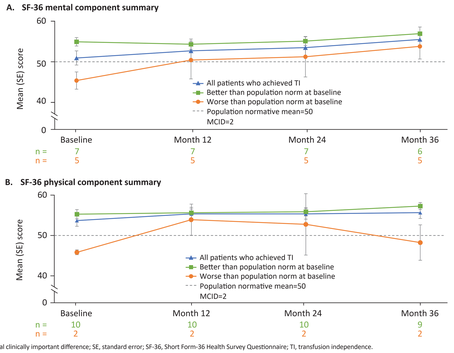
Phase 1/2 studies

- In phase 1/2 studies, prior to making improvements to the drug manufacturing process for phase 3 studies, 68.2% (15/22) of patients achieved TI, and median (min, max) weighted average Hb during TI was 10.50 g/dL (9.1, 13.2)
  - 14 of these patients sustained TI through last follow-up, which was up to 9 years
  - One patient, with human immunodeficiency virus complicated by gastrointestinal infection and bleeding, no longer meets protocol-defined TI as a result of Hb level <9 g/dL at year 6. PB VCN was stable with continued HbA^{T87Q} production. The patient is not receiving transfusions as of last follow-up (late-breaking data)

Health-related quality of life

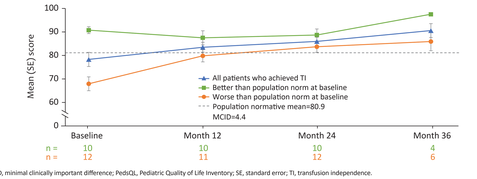
- Clinically meaningful improvements (mean score increase >2) were reported in Short Form-36 Health Survey Questionnaire mental and physical component summary scores at month 36 (**Figure 4**)
  - 1 of the 2 patients with physical component summary scores worse than the population norm at baseline reported a recent fracture prior to data capture at month 36
- Mean pediatric HRQOL scores also showed clinically meaningful improvement at month 36 (**Figure 5**)
- In adult and pediatric patients who achieved TI, mean HRQOL scores increased numerically across all other measures except for the EQ-5D-3L composite index score, for which there was little change from baseline (**Table 5**)

Figure 4. SF-36 scores over time



MCID, minimal clinically important difference; SE, standard error; SF-36, Short Form-36 Health Survey Questionnaire; TI, transfusion independence.

Figure 5. PedsQL total score over time



MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SE, standard error; TI, transfusion independence.

Table 5. Change from baseline to months 24 and 36 in patient-reported HRQOL for patients treated with beti-cel who achieved TI

	N	Baseline, mean (SE)	N	Month 24, mean (SE)	N	Month 36, mean (SE)
Adult HRQOL measures[a]						
FACT						
FACT-BMT total score	11	125.76 (11.27)	11	+3.12 (8.99)	10	+5.68 (12.29)
FACT-G total score	11	94.21 (8.60)	11	+1.59 (7.58)	10	+3.02 (8.53)
EQ-5D-3L						
Composite index score	12	0.92 (0.04)	12	+0.04 (0.04)	11	+0.03 (0.06)
Health state today	12	85.17 (3.02)	12	+7.83 (3.97)	11	+6.91 (4.0)
Pediatric HRQOL measures[b]						
PedsQL[c]						
Physical health summary score	22	81.11 (2.89)	22	+2.98 (3.20)	10	+14.69 (3.52)
Psychosocial health summary score	22	76.82 (3.23)	22	+10.15 (3.58)	10	+15.83 (3.74)
EQ-5D-Y						
Health state today	15	81.53 (4.66)	15	+9.33 (4.98)	5	+13.00 (6.64)

[a]Data from studies HGB-204, HGB-207, and HGB-212 in the subgroup of adult patients (≥18 years of age) who achieved and maintained TI through last follow-up. [b]Data from studies HGB-204, HGB-207, and HGB-212 in the subgroup of patients (<18 years of age) who achieved and maintained TI through last follow-up. [c]MCID=4.4; population normative mean=80.9.
EQ-5D-3L, EuroQol 5 Dimensions 3 Levels questionnaire; EQ-5D-Y, EuroQol 5 Dimensions Youth questionnaire; FACT, Functional Assessment of Cancer Therapy; FACT-BMT, FACT-Bone Marrow Transplantation; FACT-G, FACT-General; HRQOL, health-related quality of life; MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SE, standard error; TI, transfusion independence.

Safety

- Overall, 19.0% (12/63) of patients experienced ≥1 beti-cel–related adverse event (AE) (**Table 6**), the most common of which were abdominal pain and thrombocytopenia
- Most beti-cel–related AEs were reported in the first 24 months after infusion; none were reported after 48 months
- Five patients experienced serious veno-occlusive liver disease (only 1 had received prophylaxis) assessed as related to busulfan; all 5 received defibrotide and recovered
- No malignancies, insertional oncogenesis, or vector-derived replication-competent lentivirus were reported

Table 6. Summary of beti-cel–related AEs by age

	Adult, ≥18 y (n=31)	Adolescent, ≥12 and <18 y (n=16)	Pediatric, <12 y (n=16)	Overall (N=63)
Any related AE, n (%)	6 (19.4)	3 (18.8)	3 (18.8)	12 (19.0)
Abdominal pain	3 (9.7)	2 (12.5)	0	5 (7.9)
Thrombocytopenia	2 (6.5)	0	1 (6.3)	3 (4.8)
Dysplasia	0	1 (6.3)	0	1 (1.6)
Dyspnea	1 (3.2)	0	0	1 (1.6)
Hot flush	1 (3.2)	0	0	1 (1.6)
Immune thrombocytopenia	1 (3.2)[a]	0	0	1 (1.6)[a]
Focal nodular hyperplasia	0	0	1 (6.3)	1 (1.6)
Leukopenia	1 (3.2)	0	0	1 (1.6)
Neutropenia	1 (3.2)	0	0	1 (1.6)
Noncardiac chest pain	1 (3.2)	0	0	1 (1.6)
Pain in extremity	1 (3.2)	0	0	1 (1.6)
Tachycardia	0	0	1 (6.3)	1 (1.6)

[a]Occurred between months 24 and 36.
AE, adverse event.

CONCLUSIONS

- Beti-cel efficacy was durable up to 9 years post infusion, with no loss of TI due to loss of expression
- The majority of patients treated with beti-cel achieved TI with a safety profile consistent with known side effects of hematopoietic stem cell collection and the busulfan conditioning regimen
- Cell collection, safety and efficacy outcomes, and DP characteristics with beti-cel treatment were generally similar across study, genotype, and age subgroups in the phase 3 studies
- Improvements in HRQOL were demonstrated in both adult and pediatric patients up to 36 months
- Beti-cel is a potentially curative gene therapy for patients with TDT across ages and genotypes through achievement of TI and normal or near-normal Hb
- These data will inform real-world beti-cel treatment decisions for patients with TDT across genotypes and different age groups

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