Betibeglogene Autotemcel (Beti-cel) Gene Addition Therapy Results in Durable Hemoglobin A (HbA) Production With up to 10 Years of Follow-Up in Participants With Transfusion-Dependent β Thalassemia

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Introduction and Objectives

- Betibeglogene autotemcel (beti-cel) is an approved gene addition therapy for adult and pediatric patients with transfusion-dependent β-thalassemia (TDT)[1]

- Objectives
  - To report long-term outcomes of participants treated with beti-cel with up to 10 years of follow-up
  - To assess iron status in a subanalysis of participants who achieved transfusion independence (TI) and discontinued chelation therapy

1. Zynteglo (betibeglogene autotemcel). Prescribing information. bluebird bio, Inc.; 2022.

Baseline Characteristics for Participants Treated in Beti-cel Studies

Parameter	Phase 1/2 HGB-204 (N=18)	Phase 1/2 HGB-205 (N=4)	Phase 3 HGB-207 (N=23)	Phase 3 HGB-212 (N=18)	All 4 studies (N=63)
Sex, n (%)					
Female	13 (72.2)	2 (50.0)	12 (52.2)	8 (44.4)	35 (55.6)
Male	5 (27.8)	2 (50.0)	11 (47.8)	10 (55.6)	28 (44.4)
Age at consent, n (%)					
Adult, ≥18 years	15 (83.3)	2 (50.0)	9 (39.1)	5 (27.8)	31 (49.2)
Adolescent, ≥12 to <18 years	3 (16.7)	2 (50.0)	6 (26.1)	5 (27.8)	16 (25.4)
Pediatric, <12 years	0	0	8 (34.8)	8 (44.4)	16 (25.4)
Genotype , n (%)					
Non-β^0/β^0 [a]	10 (55.6)	4 (100)	23 (100)	6 (33.3)	43 (68.3)
β^0/β^0	8 (44.4)	0	0	12 (66.7)	20 (31.7)
αα/α-	3 (16.7)	0	1 (4.3)	2 (11.1)	6 (9.5)
Iron status, median (range)					
LIC, mg Fe/g dw	5.7 (0.4-26.4)	11.2 (3.9-14.0)	5.3 (1.0-41.0)	3.5 (1.2-13.2)	5.3 (0.4-41.0)
Cardiac T2*, msec	35 (10-54)	33 (29-46)	36.7 (21-57)	37 (15-75)	36.1 (10-75)
Ferritin, pmol/L	3147 (748-8629)[b]	4185 (2139-7097)	4438 (784-22517)	3275 (1279-8874)	3519 (748-22517)[c]

[a]Includes non-β^0/β^0 participants phenotypically similar to β^0/β^0 (IVS-1-110 homozygous or IVS-1-110/β^0 genotype).
[b]n=17. [c]n=62.
dw, dry weight; LIC, liver iron content.

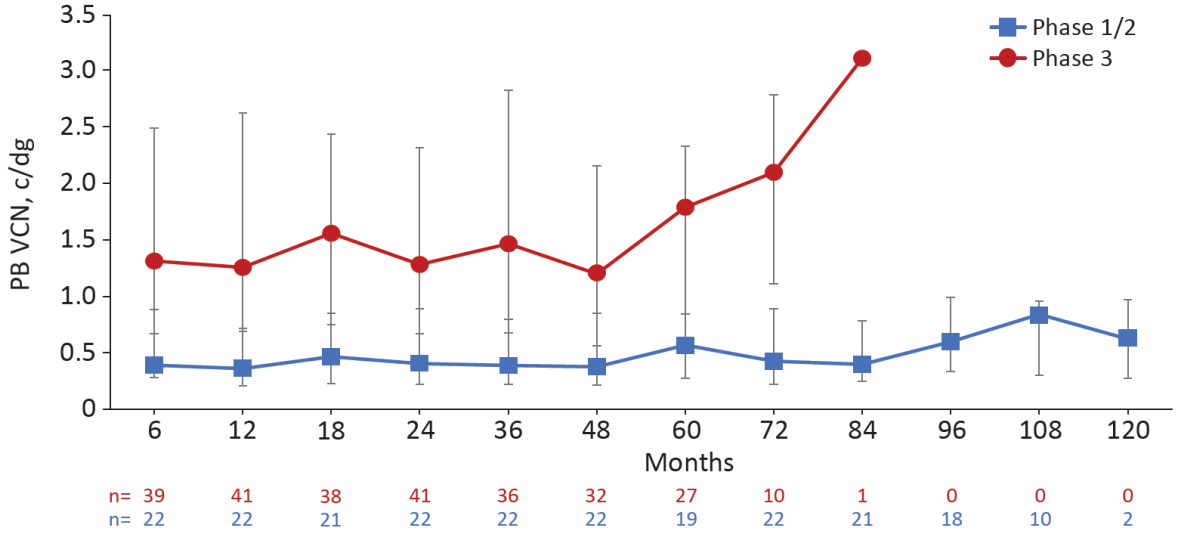
Transduction Efficiency, Engraftment, and Pharmacodynamics

	Adult, ≥18 years (n=31)	Adolescent, ≥12 to <18 years (n=16)	Pediatric, <12 years (n=16)	All 4 studies (N=63)
Number of mobilization cycles, n (%)				
1 cycle	22 (71.0)	14 (87.5)	14 (87.5)	50 (79.4)
2 cycles[a]	9 (29.0)	2 (12.5)	2 (12.5)	13 (20.6)
DP cells transduced, median (min, max), %	53.0 (18, 90)	80.5 (17, 90)	72.2 (34, 94)	64.6 (17, 94)
Month 6 PB VCN, median (min, max), c/dg	0.9 (0.1, 3.4)	1.8 (0.1, 4.7)	0.8 (0.2, 3.3)	0.9 (0.1, 4.7)
Month 6 HbA^{T87Q}, median (min, max), g/dL	5.4 (0.4, 12.0)	8.3 (1.0, 10.6)	7.9 (0.0, 10.5)	7.8 (0.0, 12.0)

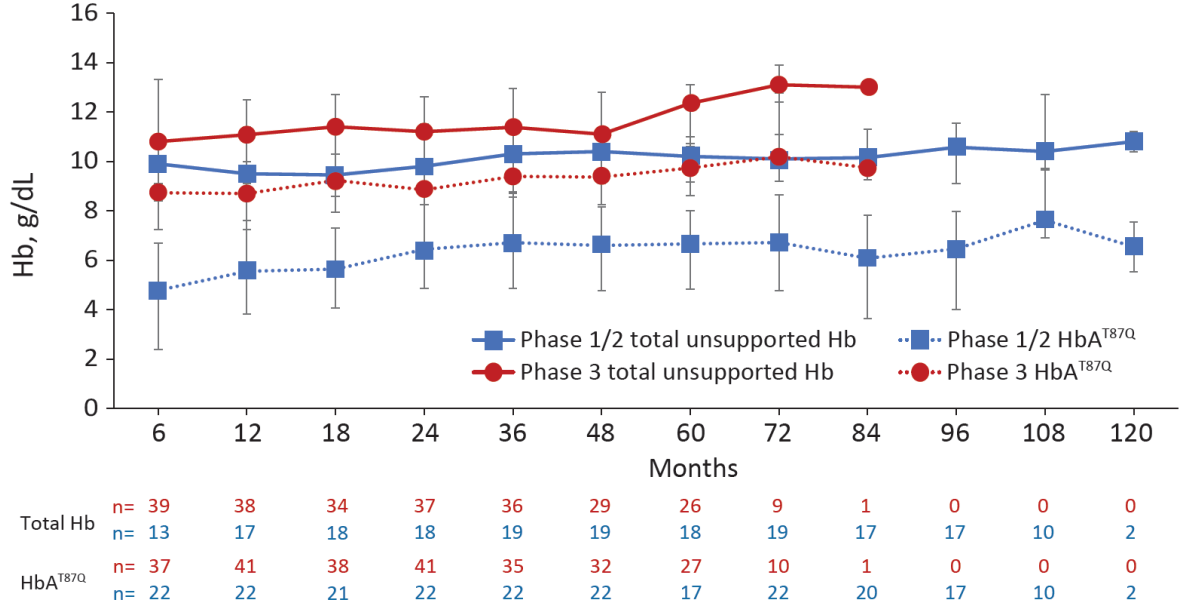
[a]One participant needed 3 mobilization cycles, but cells from only 2 of these were used for DP manufacturing.
DP, drug product; HbA, adult hemoglobin; PB peripheral blood; VCN, vector copy number.

Pharmacodynamic Variables

A. PB VCN following beti-cel treatment



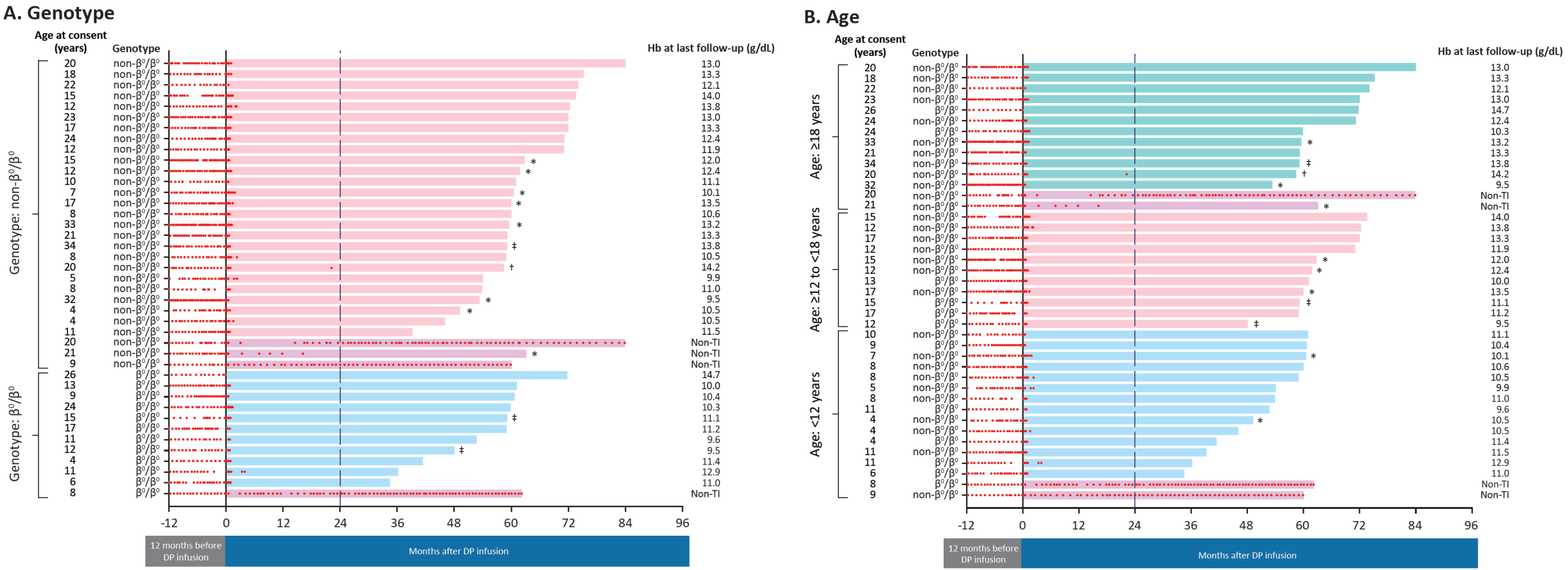
B. Total unsupported Hb and gene therapy-derived HbA^{T87Q}



- At last follow-up, median (min, max) PB VCN was 0.4 (0.1, 4.9) c/dg and 1.6 (0.1, 4.8) c/dg in phase 1/2 and phase 3, respectively, and HbA^{T87Q} was 6.6 (0.2, 10.8) and 9.7 (1.0, 14.3)

Data presented as median (Q1, Q3).
Hb, hemoglobin; HbA, adult hemoglobin; PB, peripheral blood; Q1, quartile 1; Q3, quartile 3; VCN, vector copy number.

Achievement and Maintenance of Transfusion Independence by Genotype and Age (Phase 3 Study Participants)



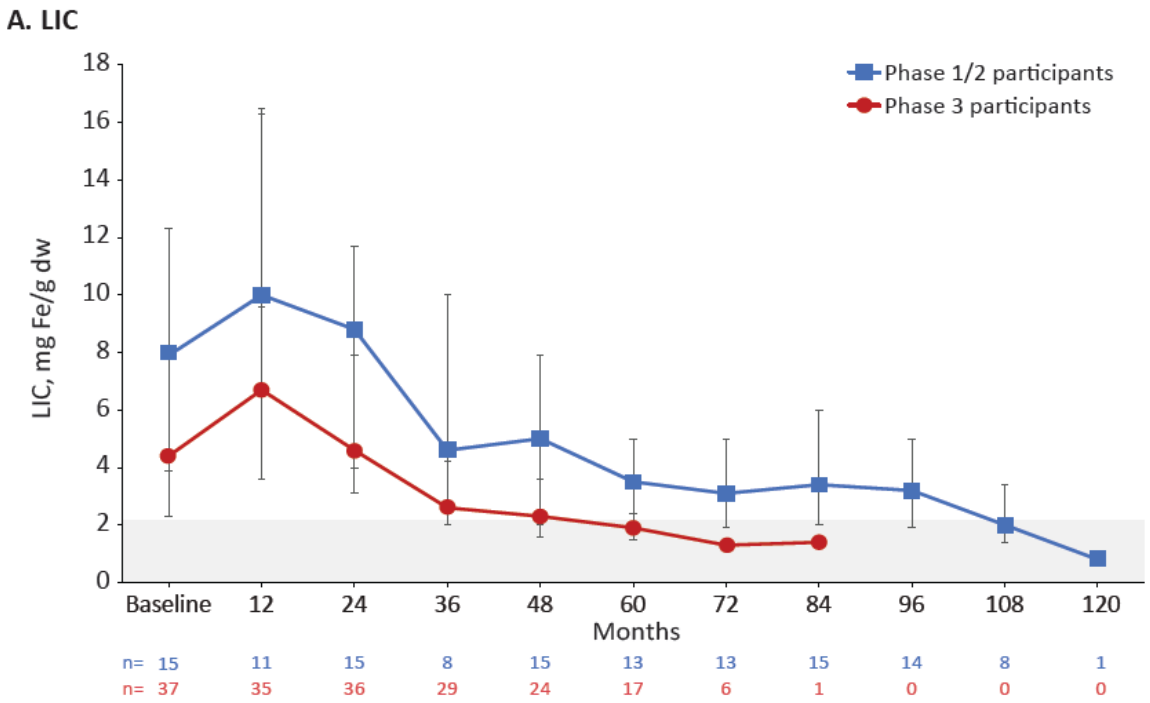
*Identifies 8 non-β^0/β^0 participants phenotypically similar to β^0/β^0 (IVS 1-110 G>A homozygous or IVS 1-110 G>A/β^0 genotype). ‡Identifies αα/α- participants. †After a planned orthopedic surgery, the participant had blood loss that required 1 pRBC transfusion. Numbers displayed at end of lanes represent 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. Transfusion independence defined as weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 months.
DP, drug product; Hb, hemoglobin; pRBC, packed red blood cell.

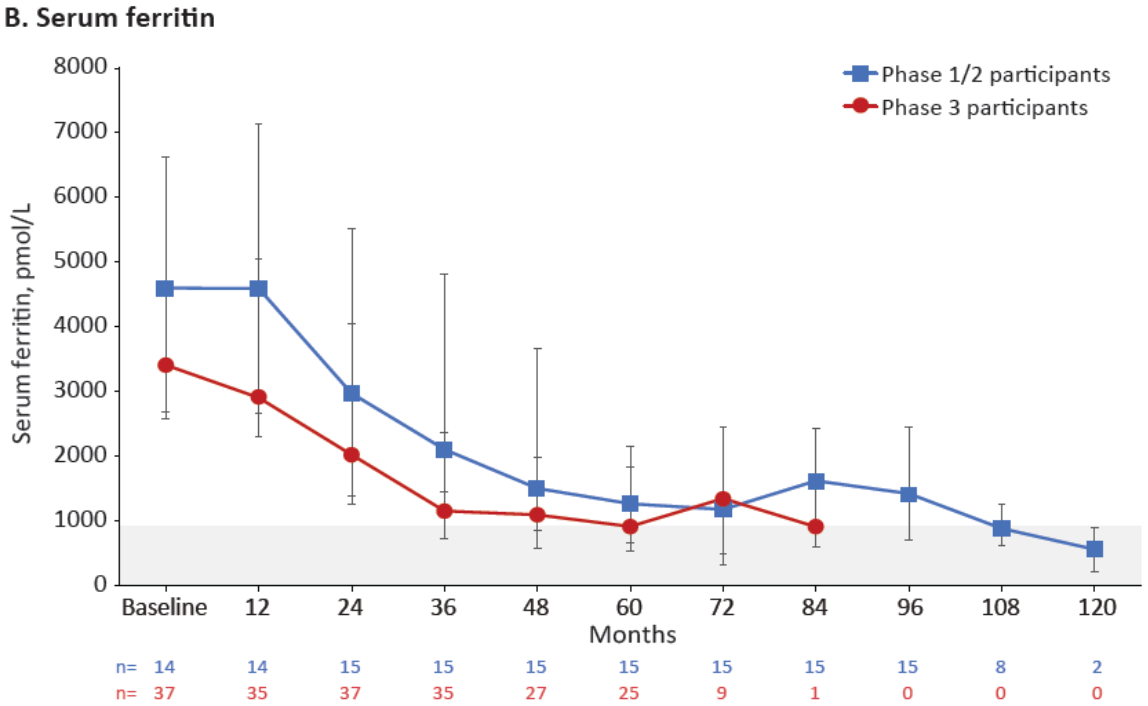
Achievement and Maintenance of Transfusion Independence by Study, Genotype, and Age (Phase 3 Study Participants)

	N	TI rate, n/N (%)	Weighted average Hb during TI, median (min, max), g/dL
Phase 3 participants	41	37/41 (90.2)	11.2 (9.8, 13.9)
By study			
HGB-207	23	21/23 (91.3)	12.0 (9.8, 13.1)
HGB-212	18	16/18 (88.9)	10.5 (9.8, 13.9)
By genotype			
Non-β^0/β^0	29[a]	26/29 (89.7)	12.0 (9.8, 13.4)
β^0/β^0	12	11/12 (91.7)	10.6 (9.8, 13.9)
By age			
Adult, ≥18 years	14	12/14 (85.7)	12.7 (9.8, 13.9)
Adolescent, ≥12 to <18 years	11	11/11 (100)	11.9 (10.0, 13.3)
Pediatric, <12 years	16	14/16 (87.5)	10.5 (9.8, 11.4)

[a]Includes 8 participants with $\beta^0/\beta^{+IVS\text{-}I\text{-}110}$ or $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$, which are phenotypically similar to participants with β^0/β^0.
Hb, hemoglobin; TI, transfusion independence.

Markers of Iron Overload in Participants Who Achieved Transfusion Independence

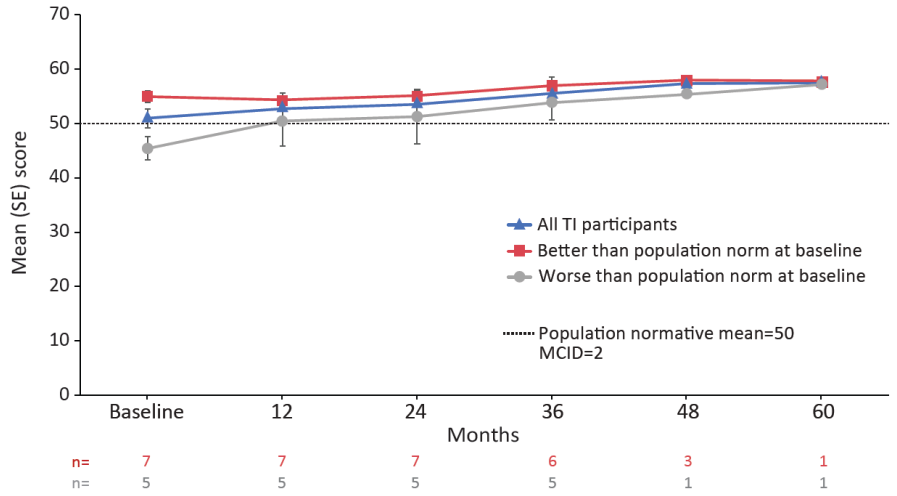




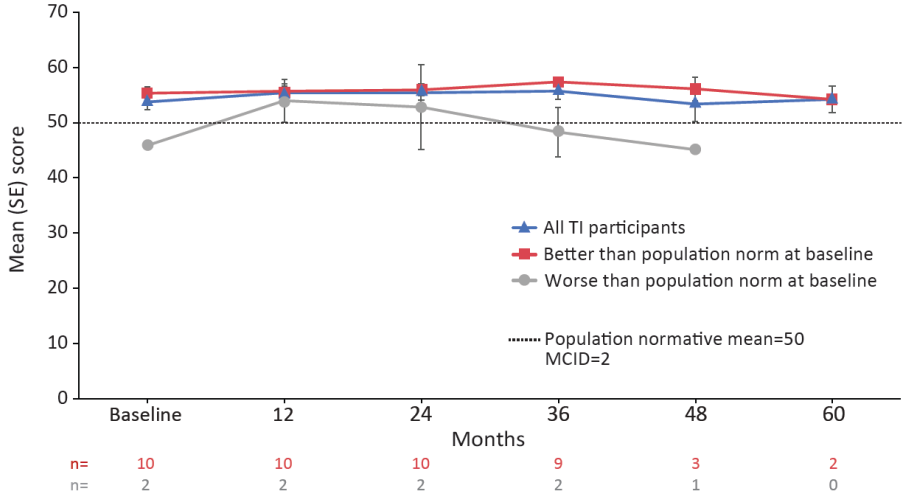
Data presented as median (Q1, Q3). Gray shading represents normal range.
dw, dry weight; LIC, liver iron concentration; Q1, quartile 1; Q3, quartile 3.

Long-Term HRQOL in Participants With Transfusion Independence

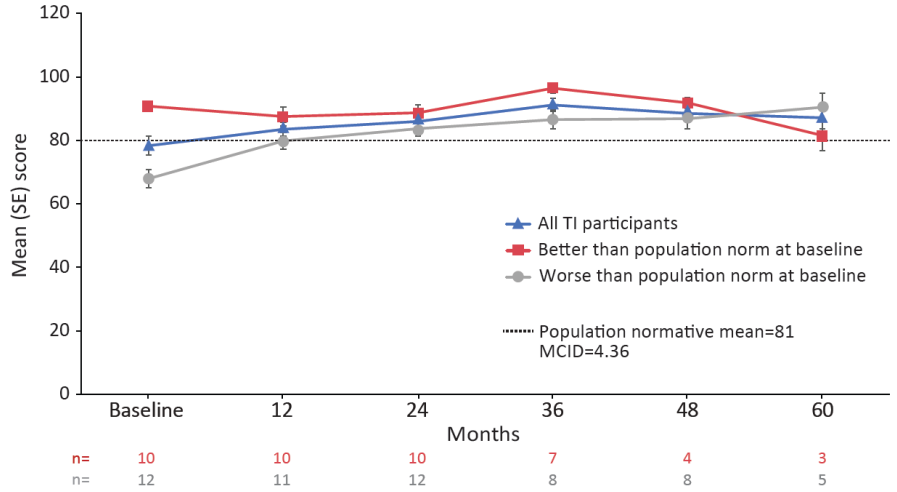
A. SF-36 mental component summary



B. SF-36 physical component summary[a]



C. PedsQL total score



[a]1 participant with physical component summary scores who had worse than the population norm at baseline reported a recent fracture prior to data capture at month 36.
HRQOL, health-related quality of life; MCID, minimal clinically important difference; PedsQL, Pediatric Quality of Life Inventory; SE, standard error; SF-36, Short Form-36; TI, transfusion independence.

Beti-cel–Related and Serious AEs >2 Years Post Beti-cel Infusion

Preferred term	Participants, n (%) (N=63)
Possibly beti-cel related[a]	
Focal nodular hyperplasia[b]	1 (1.6)
Immune thrombocytopenia	1 (1.6)
Serious AEs	
Bacillus bacteremia	1 (1.6)
Cholelithiasis	1 (1.6)
Diabetic ketoacidosis	1 (1.6)
Ectopic pregnancy	1 (1.6)
Epstein-Barr virus infection	1 (1.6)
Fetal death	1 (1.6)
Gallbladder enlargement	1 (1.6)
Gallbladder polyps	1 (1.6)
Gastritis	1 (1.6)
Gonadotropin deficiency	1 (1.6)
Influenza	1 (1.6)
Major depression	1 (1.6)
Neutropenia	1 (1.6)
Placental polyp	1 (1.6)
Pulmonary embolism	1 (1.6)
Pyrexia	1 (1.6)
Thrombocytopenia	1 (1.6)

[a]The study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the study treatment product. [b]Reported between 24 and 36 months post beti-cel infusion; an increase in size and number of hepatic nodules was reported for this participant between 36 and 48 months post beti-cel infusion.
AE, adverse event.

Conclusions

- Beti-cel is a potentially curative gene addition therapy for patients with TDT with durable efficacy up to 10 years post infusion and no loss of TI due to loss of beti-cel efficacy
- The majority of participants 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
- Participants treated with beti-cel who achieved and maintained TI demonstrated effective restoration of iron homeostasis over time and reduced iron management burden
- Both adult and pediatric HRQOL scores remained above the normative population mean up to 60 months
- Beti-cel demonstrated durable TI, normal or near normal Hb, and a favorable long-term safety profile, providing evidence to inform real-world treatment decisions

Hb, hemoglobin; HRQOL, health-related quality of life; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence.