Improvement in Iron Burden in Patients With Transfusion-Dependent β-Thalassemia (TDT) Treated With Betibeglogene Autotemcel (Beti-cel) Gene Therapy: Up to 9 Years of Follow-Up

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Introduction

- Betibeglogene autotemcel (beti-cel) is a one-time gene therapy treatment approved by the U.S. Food and Drug Administration indicated for adult and pediatric patients with 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+ HSPCs via a third-generation, self-inactivating LVV, BB305[2]
- Although TI remains a critical component for assessing patient response to beti-cel gene therapy, other measures, including reduction of markers of iron overload and iron management burden, are important for evaluating the impact of therapy over time[2,3]
- Previously, we demonstrated that iron markers stabilized up to 7 years in patients treated with beti-cel who achieved TI[4]

HSPC, hematopoietic stem and progenitor cell; LVV, lentiviral vector; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence.

1. Zynteglo (betibeglogene autotemcel). Prescribing information. bluebird bio, Inc.; 2022. 2. Locatelli F, et al. *N Engl J Med*. 2022;386(5):415-427. 3. Thompson AA, et al. Presented at: ASH. Dec 11-14, 2021; Atlanta, GA. Oral presentation; abstract 148177. 4. Walters MC, et al. Presented at: ASH. Dec 10-13, 2022; San Diego, CA. Poster 2348.

Objectives

- To report long-term management of iron overload and change in iron burden up to 9 years post beti-cel gene therapy in patients with TDT

- To assess iron status in a subanalysis of patients who achieved TI and discontinued chelation therapy

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

Methods

- In phase 1/2 (HGB-204 [NCT01745120]; HGB-205 [NCT02151526]) or phase 3 (HGB-207 [NCT02906202]; HGB-212 [NCT03207009]) parent studies, 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[1-3]
- Patients with TDT who completed a parent beti-cel study could enroll in a long-term study (LTF-303 [NCT02633943]) for up to an additional 13 years of follow-up
- Use of iron removal therapy was at the discretion of the treating physician and could include phlebotomy and/or iron chelation therapy

Efficacy

- TI (defined as a weighted average Hb ≥9 g/dL without packed red blood cell transfusions for ≥12 months) was assessed through last follow-up

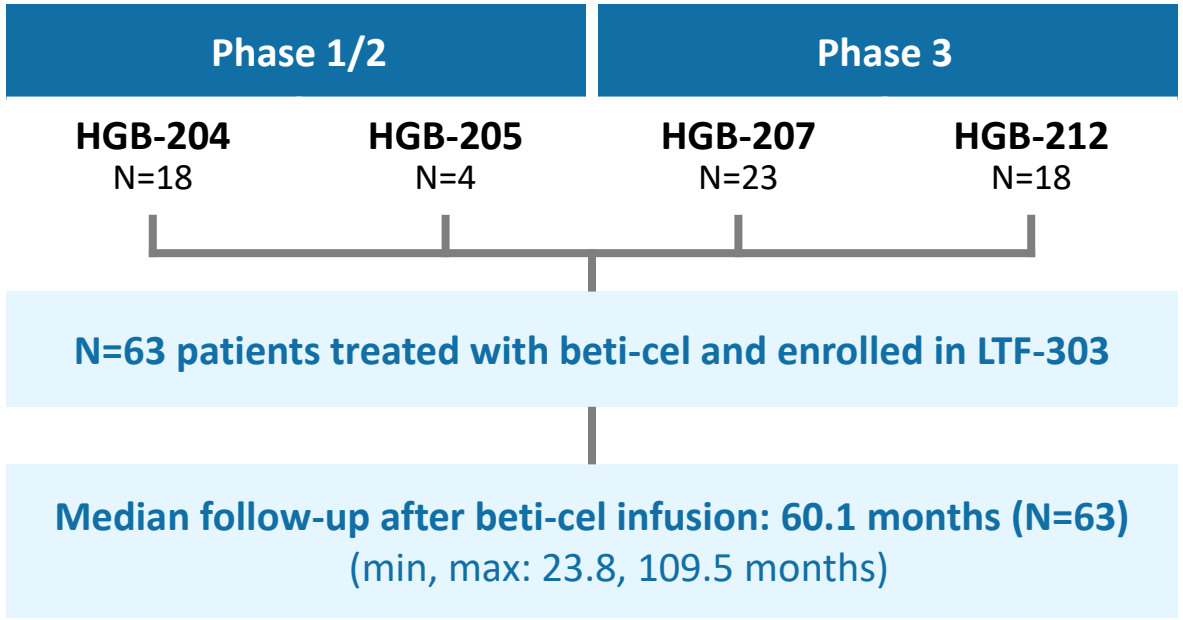
Markers of iron overload

- If 2 consecutive evaluations were within a specific range (LIC <2 mg Fe/g dw on MRI/SQUID; cardiac T2* >30 msec on cardiac MRI) at any time in the parent study or LTF-303, then the corresponding imaging study is no longer required to be performed
- Serum ferritin and TfR were assessed at regular intervals according to protocol

dw, dry weight; Hb, hemoglobin; HSPC, hematopoietic stem and progenitor cell; LIC, liver iron concentration; MRI, magnetic resonance imaging; RBC, red blood cell; SQUID, superconducting quantum interference device magnetometer; TDT, transfusion-dependent β-thalassemia; TfR, transferrin receptor; TI, transfusion independence.

1. Locatelli F, et al. *N Engl J Med*. 2022;386(5):415-427. 2. Thompson AA, et al. *N Engl J Med*. 2018;378(16):1479-1493. 3. Kwiatkowski JL, et al. Presented at: ASH; Dec 11-14, 2021; Atlanta, GA, and Virtual. Poster 3085.

Figure 1. Pooled Analysis Population and Follow-Up



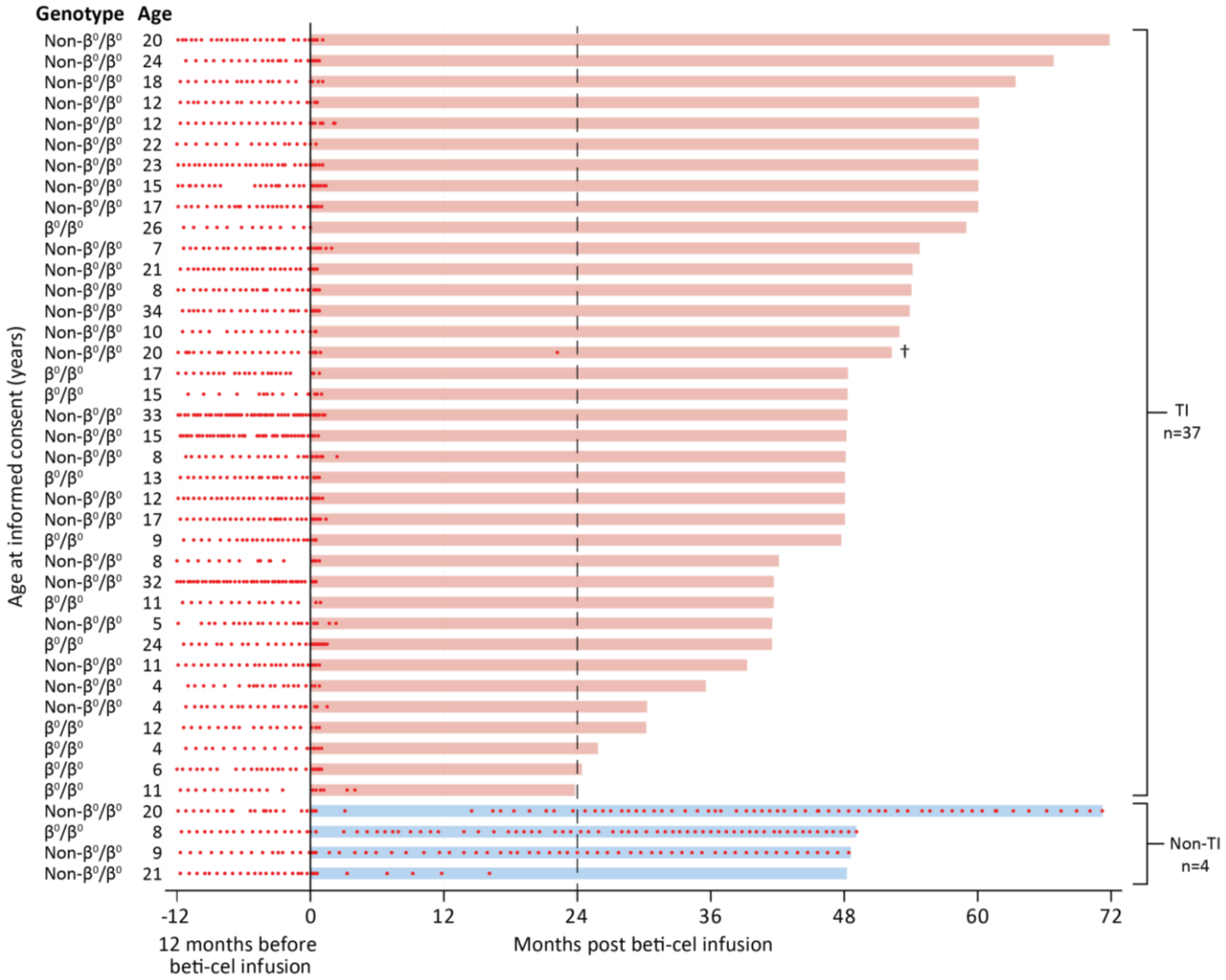
- As of January 30, 2023, 63 patients had received beti-cel in a phase 1/2 or 3 study and all are now enrolled in LTF-303

Table 1. Baseline Characteristics

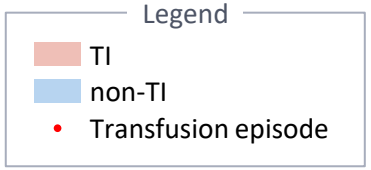
	Phase 1/2 (N=22)	Phase 3 (N=41)
Genotype, n (%)		
Non-β^0/β^0	14 (63.6)	29 (70.7)
β^0/β^0	8 (36.4)	12 (29.3)
Age at enrollment, n (%)		
Adult, ≥18 y	17 (77.3)	14 (34.1)
Pediatric, <18 y	5 (22.7)	27 (65.9)
LIC, median (min, max), mg Fe/g dw	7.1 (0.4, 26.4)	4.9 (1.0, 41.0)
Serum ferritin, median (min, max), pmol/L	3146.8 (748, 8629)	3671.9 (784, 22517)
Cardiac T2*, median (min, max), msec	34.0 (10, 54)	36.7 (15, 75)
Serum TfR, median (min, max), nmol/L	45.1 (19.9, 203.5)	103.5 (17.7, 235.3)

dw, dry weight; LIC, liver iron concentration; TfR, transferrin receptor.

Figure 2. Transfusion Status by Duration of Follow-Up (Phase 3 Studies)



- In phase 3 studies, 37/41 (90.2%) patients achieved and maintained TI through the last follow-up, with 10 patients completing their year 5 or later follow-up visit

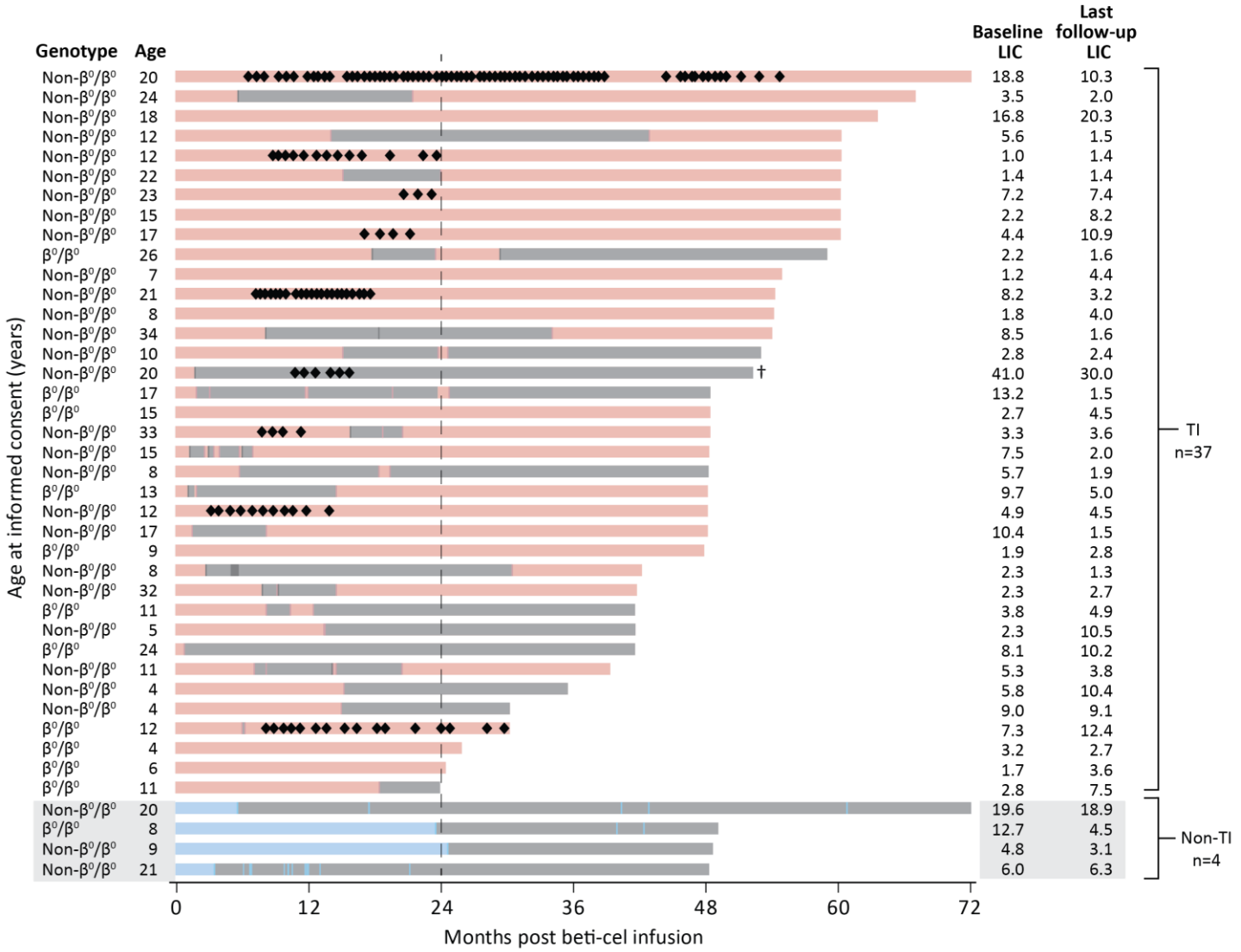


Red dots depict transfusion episodes. Vertical dashed line denotes completion of parent study and rollover to LTF-303. TI was defined as a weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 months.

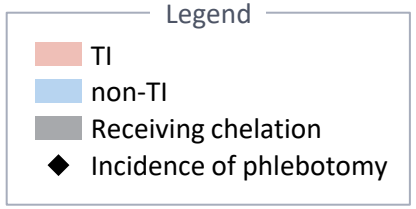
†After a planned orthopedic surgery, the patient had blood loss, which required one pRBC transfusion.

Hb, hemoglobin; pRBC, packed red blood cell; TI, transfusion independence.

Figure 3. Iron Management Status by Duration of Follow-Up (Phase 3 Studies)



- Use of iron removal therapy was at the discretion of the treating physician and could include phlebotomy and/or iron chelation therapy
- Among the 37 phase 3 TI patients:
  - 23/37 patients restarted chelation, and 9 received phlebotomy post beti-cel infusion
  - 12/23 stopped again after restarting chelation
  - 26/37 were not on chelation at last follow-up



Vertical dashed line denotes completion of parent study and rollover to LTF-303. TI was defined as a weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 months. †After a planned orthopedic surgery, the patient had blood loss, which required one pRBC transfusion.

Hb, hemoglobin; LIC, liver iron concentration; pRBC, packed red blood cell.

Transfusion Independence and Iron Management Status (Phase 1/2 Studies)

- In phase 1/2 studies, 15/22 (68.2%) patients achieved TI; 14 of these patients maintained TI through the last follow-up, which was up to 9 years
  - One patient with complicated by gastrointestinal infection and bleeding no longer meets protocol-defined TI as a result of Hb level <9 g/dL at year 6. Peripheral blood VCN was stable with continued HbA^{T87Q} production. The patient is not receiving transfusions as of last follow-up (late-breaking data)
  - All 14 patients restarted iron chelation, and 3 received phlebotomy post beti-cel infusion; 9 are no longer on chelation

Hb, hemoglobin; TI, transfusion independence; VCN, vector copy number.

Table 2. Summary of Iron Chelation Initiation[a] and Duration Among Patients Who Achieved TI in Beti-cel Studies

	Phase 1/2 (n=14)	Phase 3 (n=37)	All (N=51)
Restarted iron chelation post DPI, n	**14**	**23**	**37**
Duration of follow-up from DPI, median (min, max), months	85.8 (75.3, 109.5)	48.1 (23.8, 66.8)	53.9 (23.8, 109.5)
Time from DPI to restart of iron chelation, median (min, max), months	11.9 (1.7, 25.0)	7.8 (0.8, 17.8)	8.2 (0.8, 25.0)
Restarted then stopped iron chelation post DPI, n	**9**	**12**	**21**
Duration of follow-up from DPI, median (min, max), months	85.7 (75.3, 109.5)	48.1 (30.2, 66.8)	60.1 (30.2, 109.5)
Time from DPI to restart of iron chelation, median (min, max), months	9.0 (1.7, 25.0)	6.6 (1.1, 15.6)	7.2 (1.1, 25.0)
Time from DPI to last iron chelation use,[b] median (min, max), months	60.2 (24.2, 71.3)	20.5 (6.3, 42.9)	30.1 (6.3, 71.3)
Time from last iron chelation use to last follow-up, median (min, max), months	36.6 (11.8, 79.4)	27.5 (11.7, 45.3)	31.0 (11.7, 79.4)
Iron chelation ongoing post DPI,[c] n	**5**	**11**	**16**
Duration of follow-up, median (min, max), months	95.6 (85.2, 100.1)	41.7 (23.8, 59.0)	50.3 (23.8, 100.1)

- In total, 51 patients across phase 1/2 and 3 studies achieved and maintained TI through last follow-up
  - 37/51 patients restarted chelation, and 12 received phlebotomy post beti-cel infusion; 35 are no longer on chelation
  - 1 patient received concurrent iron chelation and phlebotomy, 1 patient had brief chelation use followed by phlebotomy, and 3 patients had phlebotomy followed by chelation

[a]Iron management was administered at the discretion of the investigator. [b]Time from DPI to last iron chelation end date. [c]Restarted iron chelation and ongoing iron chelation use as of last follow-up.
DPI, drug product infusion; Hb, hemoglobin; TI, transfusion independence; VCN, vector copy number.

Table 3. Iron and Ineffective Erythropoiesis Markers in Patients Who Achieved TI

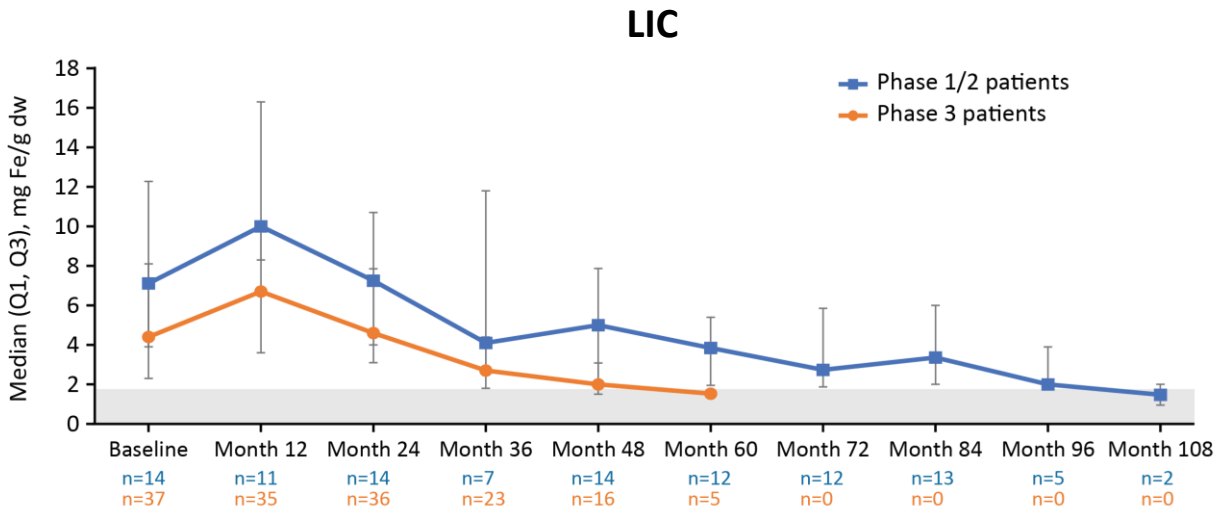
Measure	n	Baseline median (min, max)	n	Month 48 median change from baseline (min, max)
LIC, mg Fe/g dw	51	5.0 (1.0, 41.0)	30	-3.9 (-22.3, 10.5)
Serum ferritin, pmol/L	50	3756.2 (784, 13,432)	34	-2119.0 (-7211, 3889)
Cardiac T2*, msec	51	36.4 (15, 75)	34	-2119.0 (-7211, 3889)
Measure	**n**	**Baseline median (min, max)**	**n**	**Month 36 median change from baseline (min, max)**
Serum TfR, nmol/L[a]	48	85.4 (17.7, 235.3)	31	-16.13 (-168.3, 81.1)

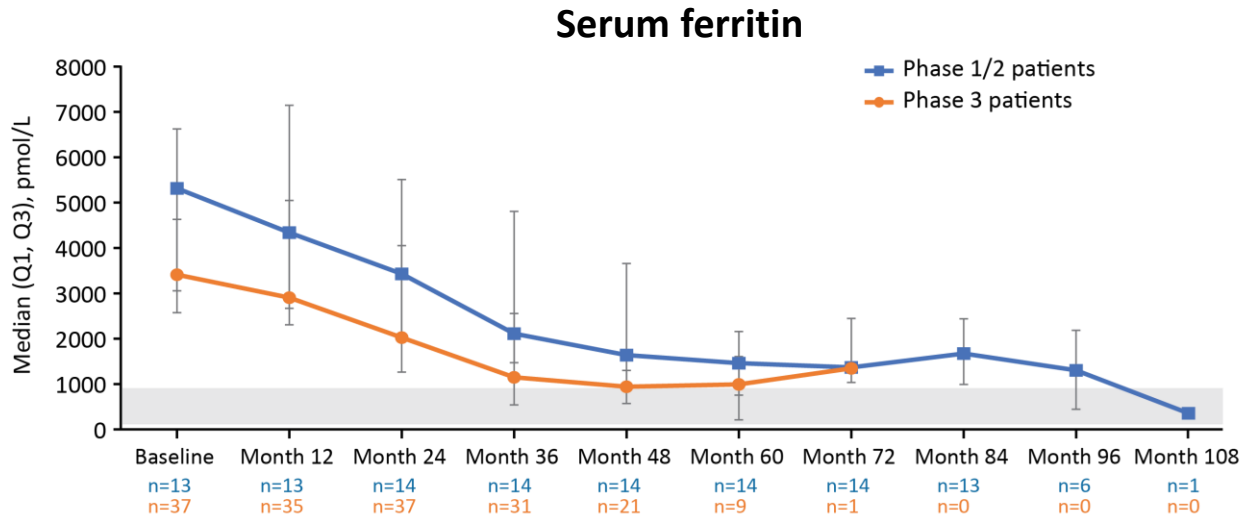
[a]Prespecified assessment at month 36.

dw, dry weight; LIC, liver iron concentration; TfR, transferrin receptor; TI, transfusion independence.

Figure 4. Iron Markers Over Time in Patients Who Achieved TI

- Reductions from baseline in serum ferritin were observed as early as month 24.
- By month 48, reductions in both LIC levels and serum ferritin were observed, and cardiac T2* remained stable.
- Reductions from baseline in serum TfR were observed at month 36

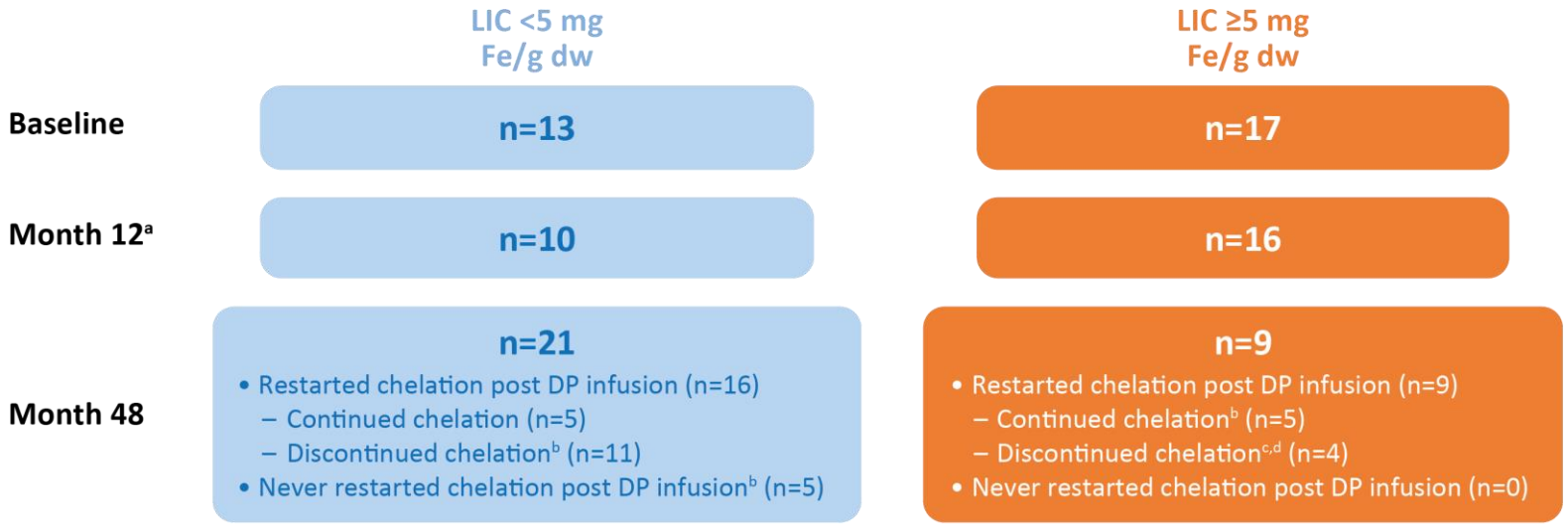




Gray shading represents normal range.
dw, dry weight; LIC, liver iron concentration; Q1, quartile 1; Q3, quartile 3; TI, transfusion independence.

Figure 5. Chelation Status by LIC Measurement at Month 48 in Patients Who Achieved TI

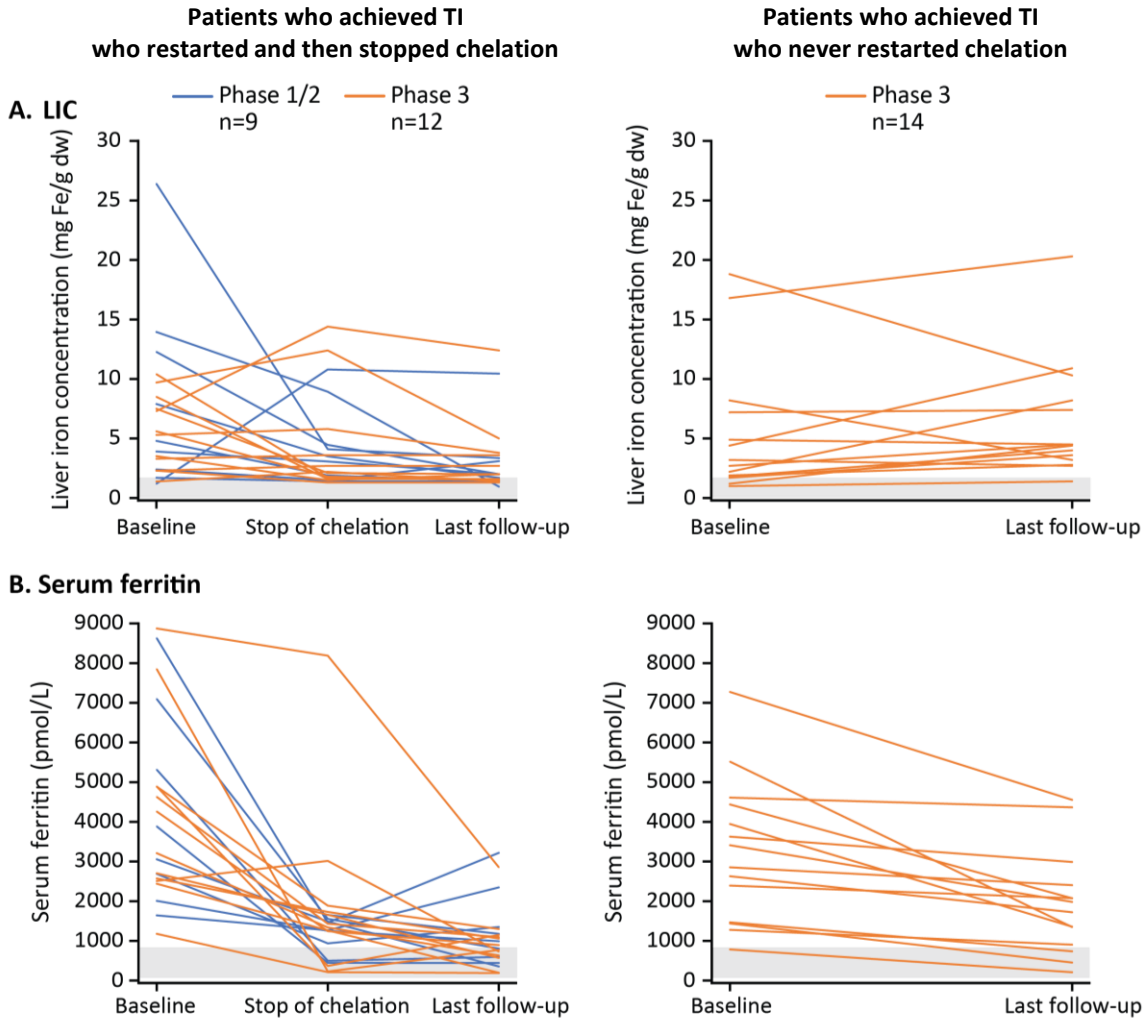
- 30/51 patients who achieved TI had an LIC measurement at month 48
  - At baseline, 13/30 (43.3%) patients had an LIC <5 and 17/30 (56.7%) had an LIC ≥5 mg Fe/g dw
  - At month 12, 10/26 (38.5%) had an LIC <5 and 16/26 (61.5%) had an LIC ≥5 mg Fe/g dw
  - At month 48, the proportion of patients with an LIC <5 Fe/g dw increased to 21/30 (70.0%) and 9/30 (30.0%) had an LIC ≥5



[a]4 patients did not have an LIC measurement at month 12. [b]1 patient had phlebotomy. [c]2 patients had phlebotomy. [d]Month 48 LIC values for the 4 patients who stopped chelation with LIC ≥5 mg Fe/g dw were 7.5, 7.9, 9.0, and 14.4 mg Fe/g dw. At last follow-up, LIC was <5 mg Fe/g dw for 3 of these patients and had increased from 7.5 to 10.5 mg Fe/g dw for the remaining patient.

DP, drug product; dw, dry weight; LIC, liver iron concentration; TI, transfusion independence.

Figure 6. Iron Markers in Patients Who Achieved TI and Were Off Chelation Therapy



dw, dry weight; LIC, liver iron concentration; TI, transfusion independence.

- Among the 35/51 patients who achieved TI and were off chelation at last follow-up, most experienced reductions in LIC and serum ferritin
- Cardiac T2* (not shown) remained stable and was >20 msec for most patients at last follow-up
- Iron management was administered at the discretion of the investigator.
  - 10/21 (47.6%) patients who received chelation received only deferasirox, 1 patient received deferoxamine and then deferiprone, and 10 (47.6%) received deferasirox and at least one other chelation agent (deferoxamine and/or deferiprone) at various times post infusion

Safety

- Overall, 12/63 (19.0%) patients experienced ≥1 beti-cel–related adverse event; the most common (occurring in ≥3 patients) were abdominal pain (5/63 [7.9%]) and thrombocytopenia (3/63 [4.8%])
- No malignancies, insertional oncogenesis, or vector-derived replication-competent lentivirus were reported
- Safety of beti-cel treatment largely reflected the known side effects of hematopoietic stem cell collection and the busulfan conditioning regimen

Conclusions

- With up to 9 years of follow-up, patients treated with beti-cel who achieved and maintained TI demonstrated effective restoration of iron homeostasis over time and reduced iron management burden

- Collectively, these results demonstrate sustained HbA^{T87Q} expression and the long-term durability and stability of TI after beti-cel gene therapy in patients with TDT and will inform real-world treatment decisions for patients with TDT

TI, transfusion independence; TDT, transfusion-dependent β-thalassemia.

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