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Restoring Iron Homeostasis in Patients Who Achieved Transfusion Independence After Treatment with Betibeglogene Autotemcel Gene Therapy: Results from Up to 7 Years of Follow-up

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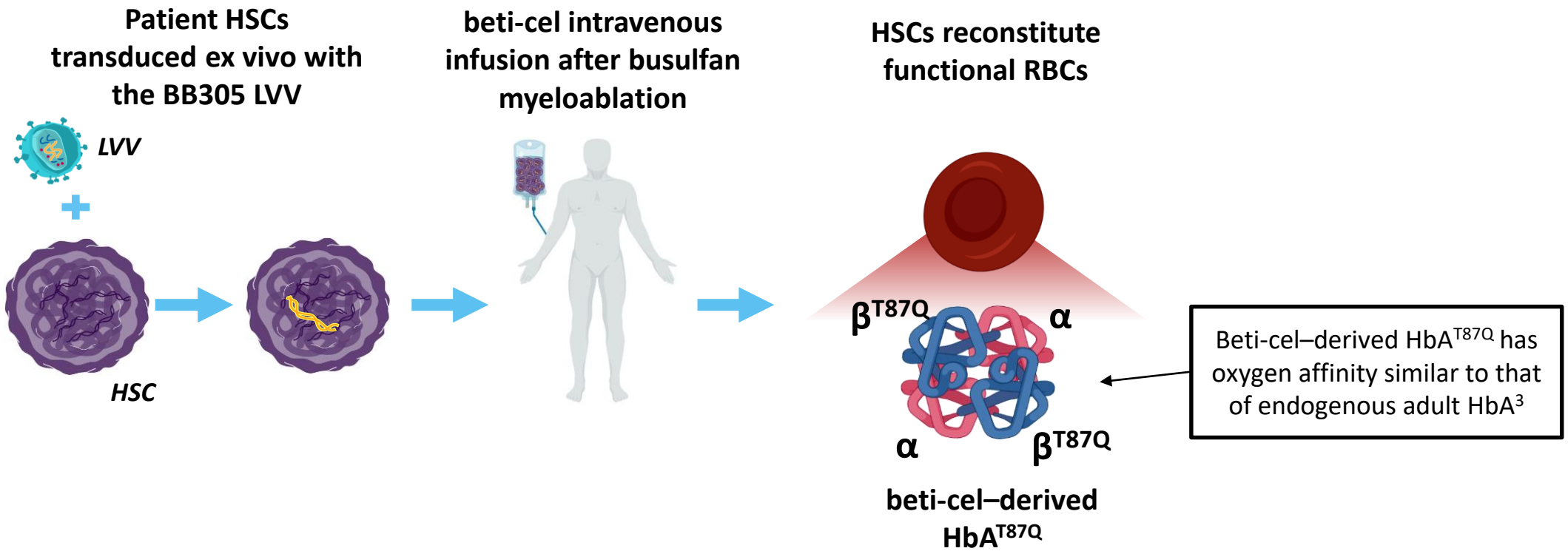
Betibeglogene autotemcel (beti-cel) ex vivo gene therapy for TDT

- Transfusion-dependent β-thalassemia (TDT) is a severe, progressive genetic disease caused by mutations in the β-globin gene resulting in absent or significantly reduced adult hemoglobin, HbA, that normally accounts for approximately 95% of the total Hb in the blood of adults after 6 months of age[1,2]

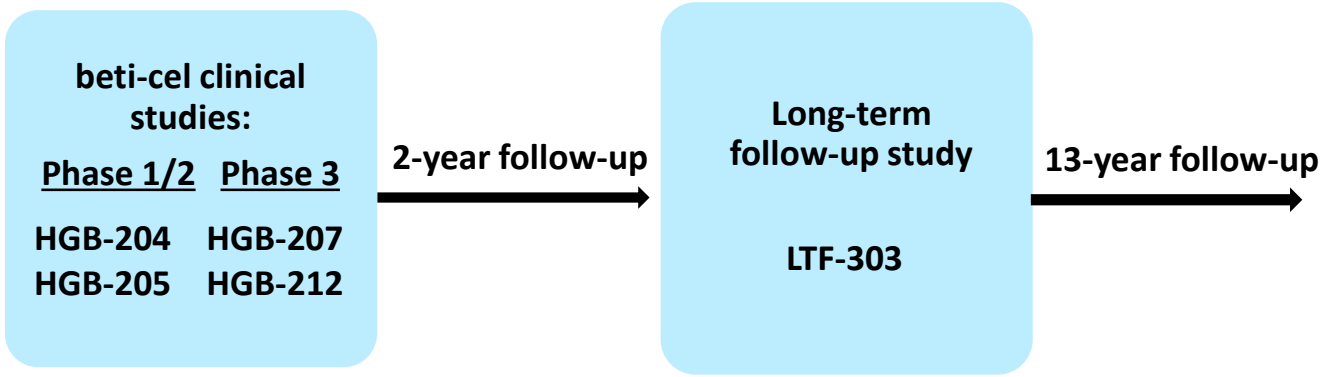


1. Paramore C, et al. *Patient.* 2021;14(2):197-208. 2. Thomas C, et al. *Continuing Education in Anaesthesia. Critical Care & Pain.* 2012;12(5):251-6. 3. Pawliuk R, et al. *Science.* 2001;294(5550):2368-71.

HbA, adult hemoglobin; Hb, hemoglobin; HSC, hematopoietic stem cell; LVV, lentiviral vector; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia.

beti-cel long-term follow-up: LTF-303 study overview

beti-cel has been studied in 4 clinical trials across all ages and genotypes; all parent studies are fully enrolled



LTF-303 endpoints

Efficacy

- Transfusion independence*
- Peripheral blood VCN, HbA^{T87Q}, total Hb
- Ineffective erythropoiesis
- Iron burden

Safety

- DP-related AEs and all SAEs
- Replication-competent lentivirus detection
- Monitoring for insertional oncogenesis

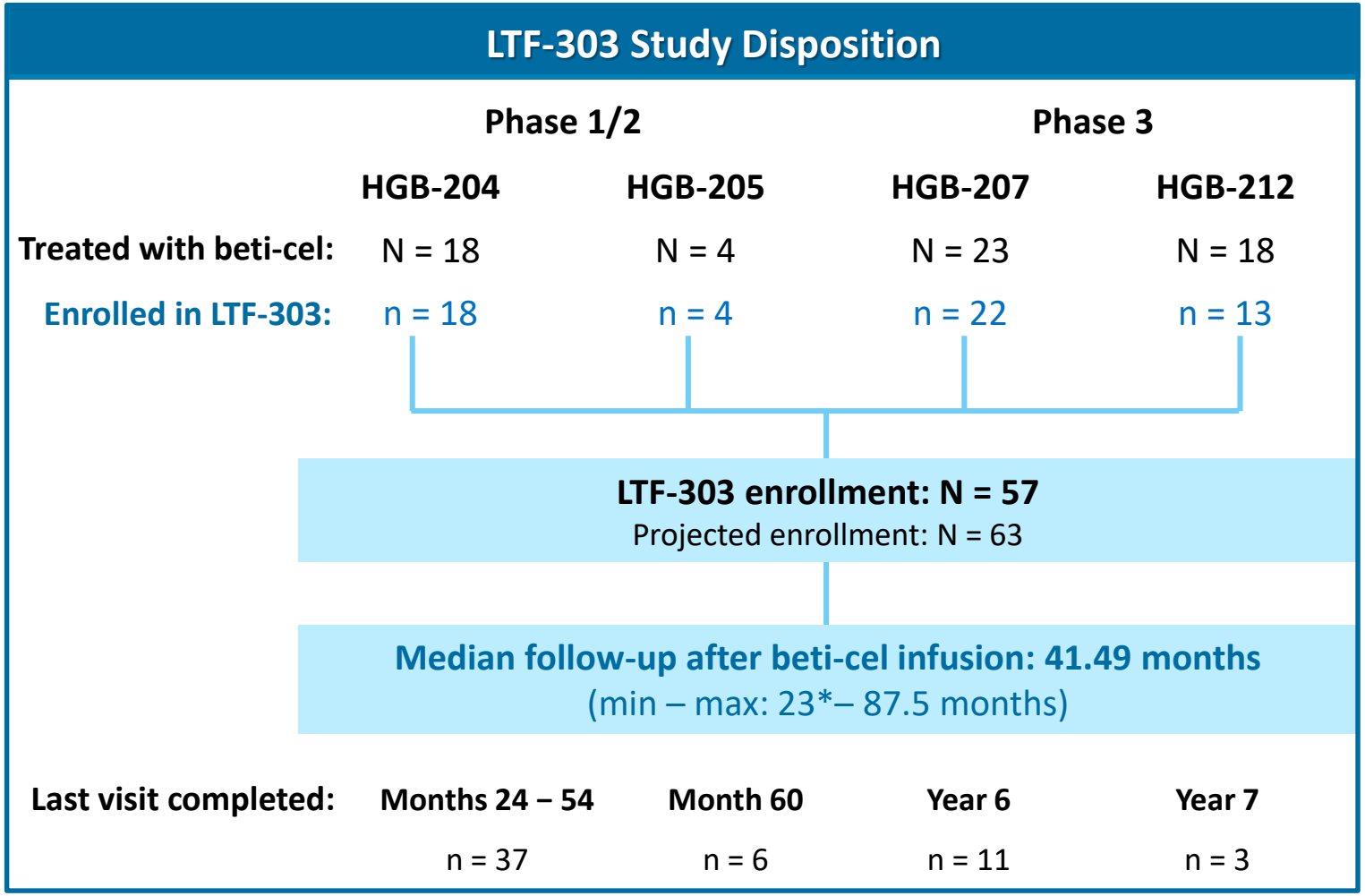
Iron management

- All patients stopped iron chelation at least 7 days prior to the start of busulfan conditioning
- Chelation could be resumed after beti-cel infusion upon recovery from conditioning at the physician's discretion
- We conducted a subanalysis of iron status that included 16 patients who achieved TI and restarted then stopped chelation, with at least 9 months of follow-up after discontinuation of chelation

*Defined as weighted average Hb ≥ 9 g/dL without pRBC transfusions for ≥ 12 months.

AE, adverse event; DP, drug product; Hb, hemoglobin; pRBC, packed red blood cell; SAE, serious adverse event; VCN, vector copy number.

LTF-303 study enrollment and follow-up



- **All patients who completed 2 years within their respective parent studies have been enrolled in LTF-303**
- **Twenty patients enrolled in LTF-303 have ≥ 5 years of follow-up**

*One patient had their Month 24 visit 23 months post-infusion.

Patient and drug product characteristics in LTF-303

Patient characteristics at baseline prior to infusion

		Phase 1/2 (N = 22)	Phase 3 (N = 35)
Genotypes, n (%)	β^0/β^0	**8** (36)	**8** (23)
	β^E/β^0	**9** (41)	**6** (17)
	β^+/β^+	**3** (14)	**8** (23)
	β^0/β^+	**1** (4.5)	**13** (37)
	β^0/β^{X}†	**1** (4.5)	**0** (0)
Age at consent prior to infusion, median (min – max), years		**20** (12 – 35)	**15** (5 – 34)
Pre-study pRBC transfusion volume,‡ median (min – max), mL/kg/yr		**171.2** (124.4 – 273.2)	**192.9** (74.6 – 276.1)
Pre-study pRBC transfusions median (min – max), transfusions/yr		**13** (10.0 – 17.5)	**17.5** (11.0 – 39.5)
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), ms		**34** (10 – 54)	**36.8** (15 – 75)
Serum ferritin, median (min – max), pmol/L		**3146.8**§ (748 – 8629)	**3671.9** (784 – 22,517)
Splenectomy, n (%)		**9** (41)	**7** (20)
Fertility preservation,‖ n (%)		**13** (59.1)	**25** (71.4)

Drug product characteristics

median (min – max)

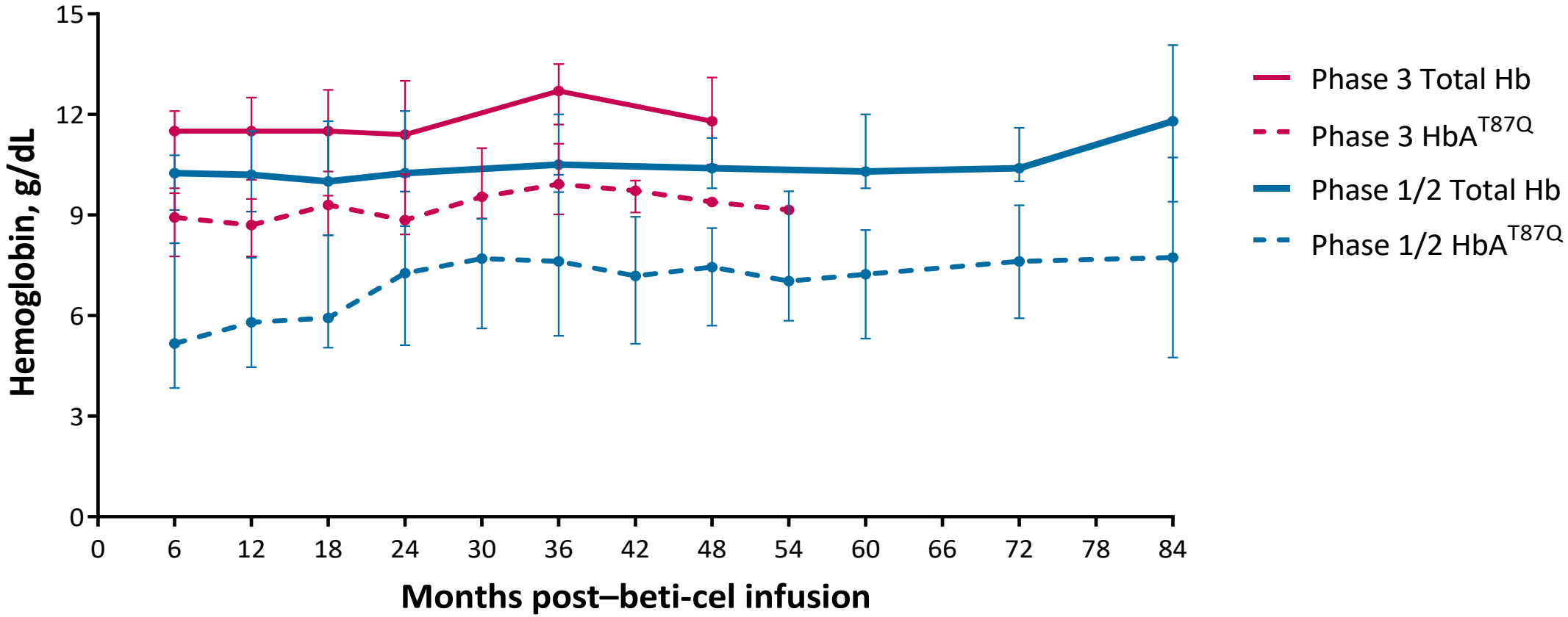
	Phase 1/2 (N = 22)	Phase 3 (N = 35)
Vector copy number, vector copies/diploid genome	**0.8** (0.3 – 2.1)	**2.9** (1.2 – 5.6)
CD34+ cells transduced, %	**32**¶ (17 – 58)	**75** (34 – 90)
Cell dose, x 10^6 CD34+ cells/kg	**8.9** (5.2 – 18.1)	**8.7** (5.0 – 19.9)

†Unknown allele is an unidentified β^+ allele since patient is producing endogenous HbA.
‡Retrospective data 2 years prior to enrollment in parent study.
¶Reported for 18/22 patients in phase 1/2 because % CD34+ cells transduced was not assessed in HGB-205.
§Reported for 21 out of 22 patients.
‖Fertility preservation was an optional procedure.

HbA, adult hemoglobin; pRBC, packed red blood cell.

Normal or near-normal Hb levels are mainly driven by HbA^{T87Q}

Unsupported total Hb and HbA^{T87Q} in patients who achieved transfusion independence

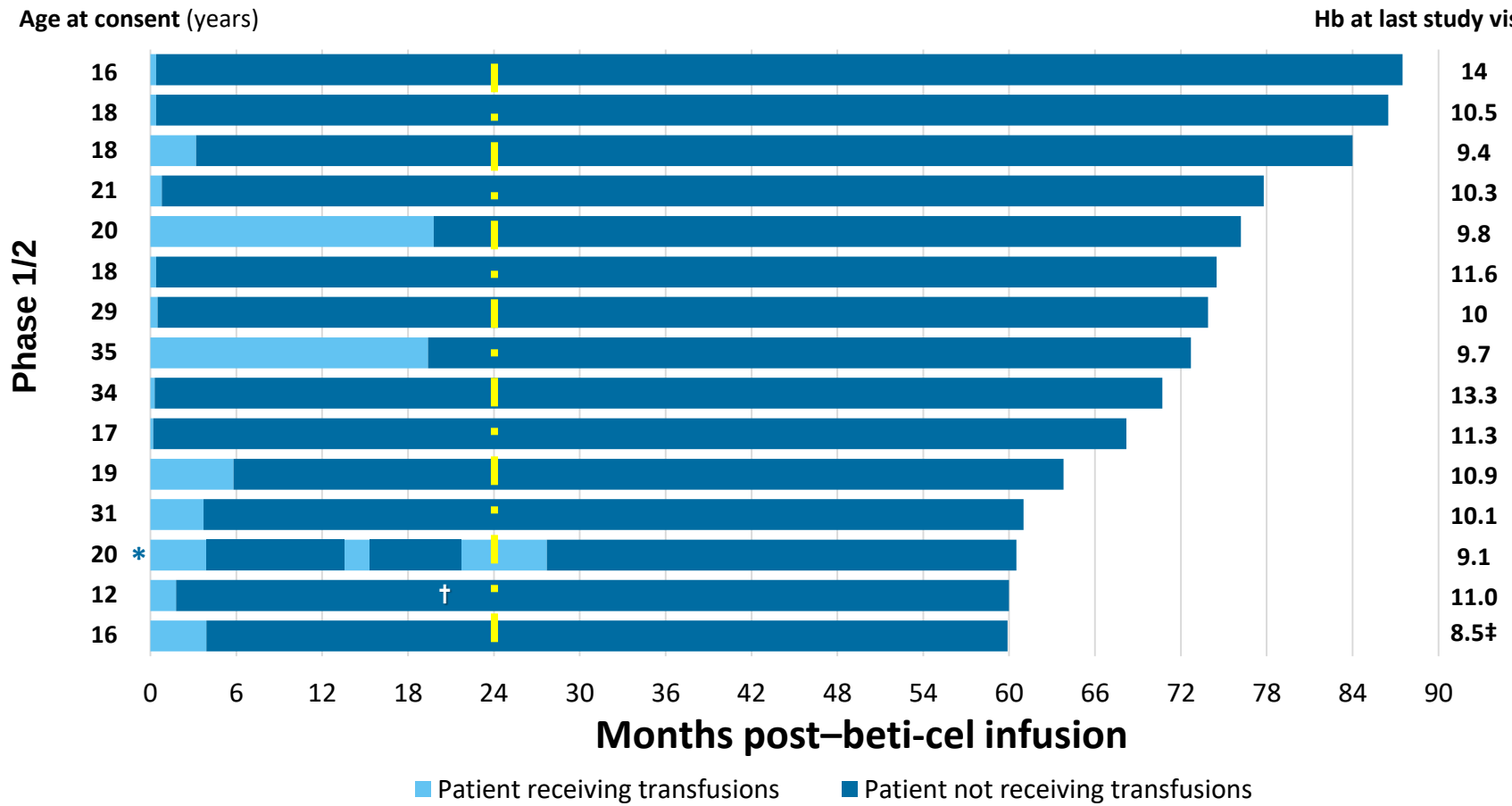


Phase 3	Total Hb, n	31	30	29	30	0	18	0	2	0	0	0	0	0	0
	HbA^{T87Q}, n	29	31	29	31	19	16	5	2	1	0	0	0	0	0
Phase 1/2	Total Hb, n	12	15	14	14	0	15	0	15	0	15	0	10	0	3
	HbA^{T87Q}, n	15	15	15	15	15	15	15	15	14	14	0	9	0	2

Unsupported Hb defined as Hb value with no transfusion in the prior 60 days. Median (Q1, Q3) depicted.
Hb, hemoglobin.

Phase 1/2 studies: maintenance of TI for up to 7 years of follow-up

Transfusion status in phase 1/2 patients enrolled in LTF-303 who achieved TI

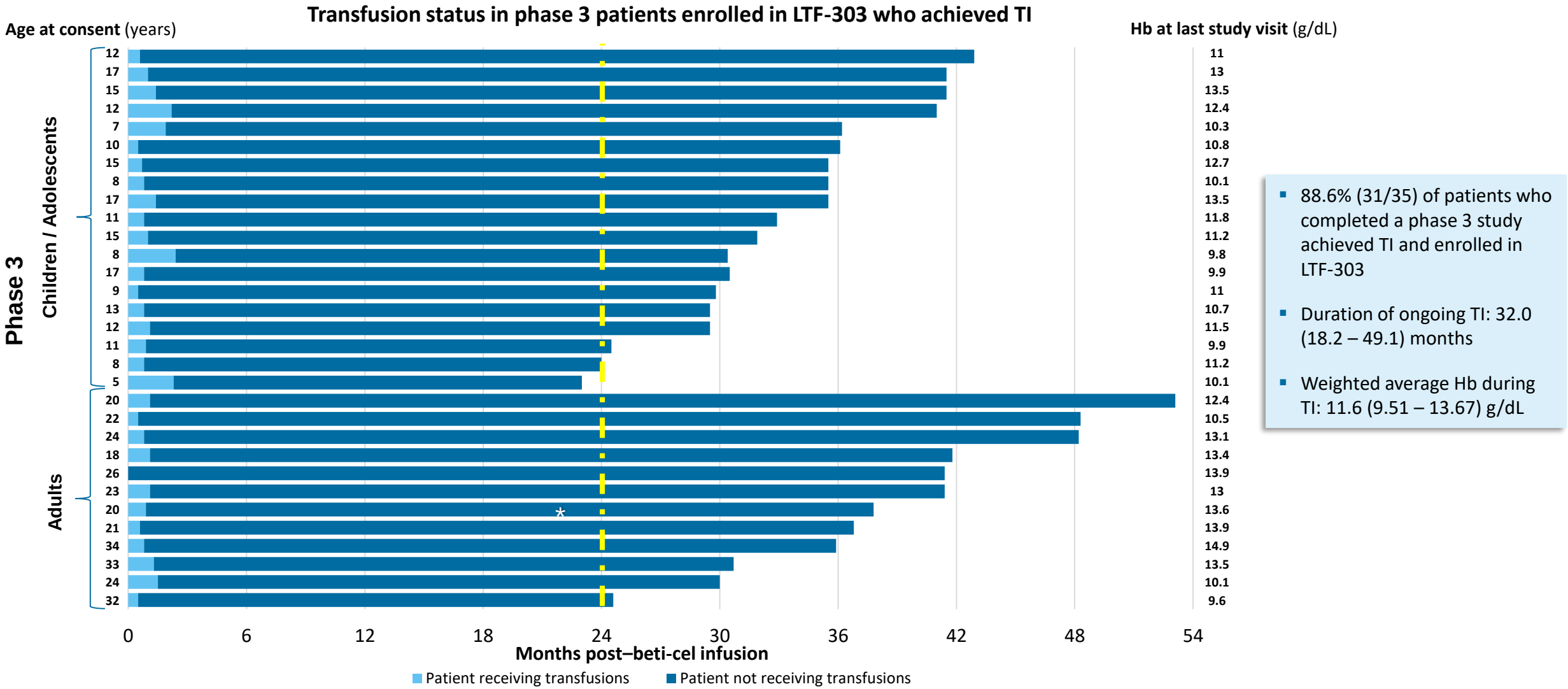


- 68.2% (15/22) of patients who completed a phase 1/2 study and enrolled in LTF-303 achieved TI
- Duration of ongoing TI: 65.91 (19.8 – 84.5) months
- Weighted average Hb during TI: 10.3 (9.1 – 13.2) g/dL

*Patient diagnosed with HIV-1 infection approximately 22 months after beti-cel infusion.
†Patient had a single transfusion for an acute event of *Bartonella* infection.
‡Represents patient's total unsupported hemoglobin at last study visit; this patient's weighted average hemoglobin during TI was 9.3 g/dL.

TI, transfusion independence (defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months).
Yellow dotted line denotes completion of parent study and enrollment in LTF-303.

Phase 3 studies: maintenance of TI for up to 4 years of follow-up



- 88.6% (31/35) of patients who completed a phase 3 study achieved TI and enrolled in LTF-303
- Duration of ongoing TI: 32.0 (18.2 – 49.1) months
- Weighted average Hb during TI: 11.6 (9.51 – 13.67) g/dL

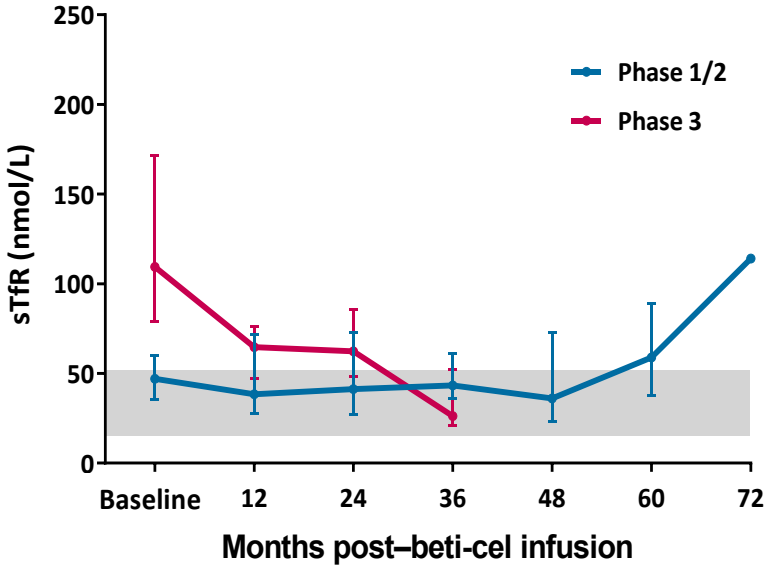
*Patient's total Hb level at Month 22 was 13.4 g/dL. After a planned orthopedic surgery, the patient had blood loss, which required 1 pRBC transfusion.

TI, transfusion independence (defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months).
Yellow dotted line denotes completion of parent study and enrollment in LTF-303.

Data as of August 18, 2021

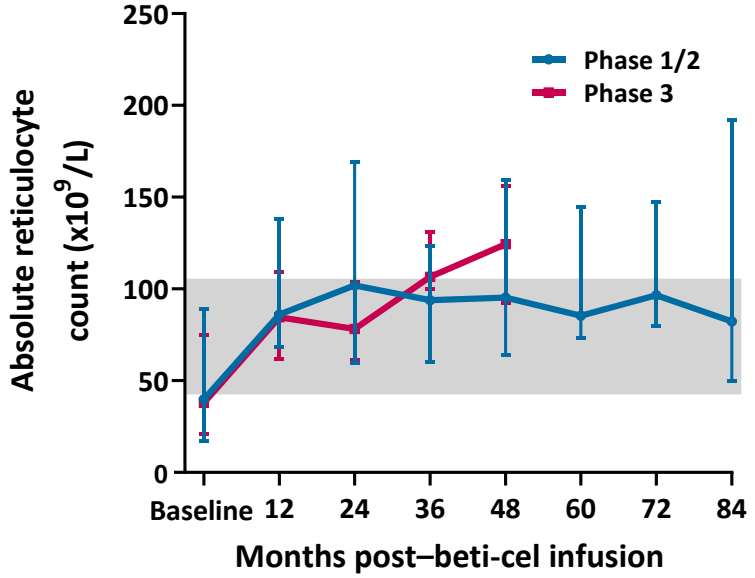
Improved erythropoiesis in patients who achieved TI

Soluble transferrin receptor



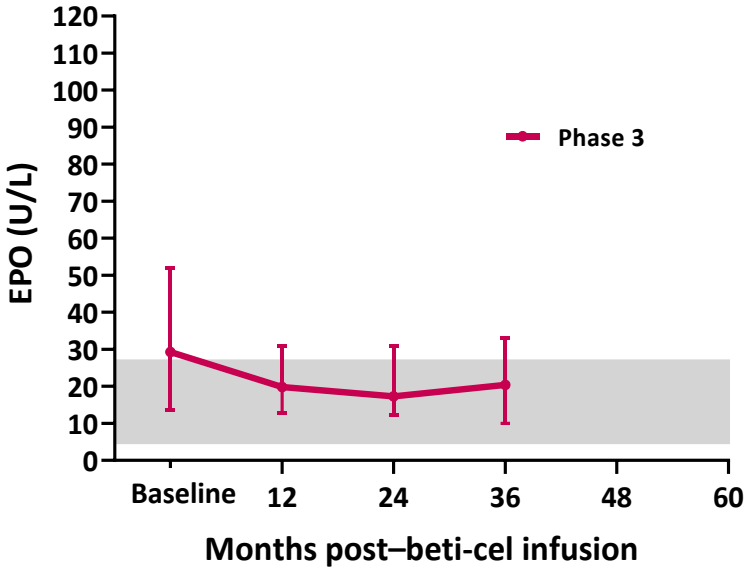
n =	11	11	12	10	4	8	1
n =	31	28	31	7	0	0	0

Reticulocyte count



n =	15	14	15	15	15	15	10	3
n =	30	29	29	29	2	0	0	0

Erythropoietin*

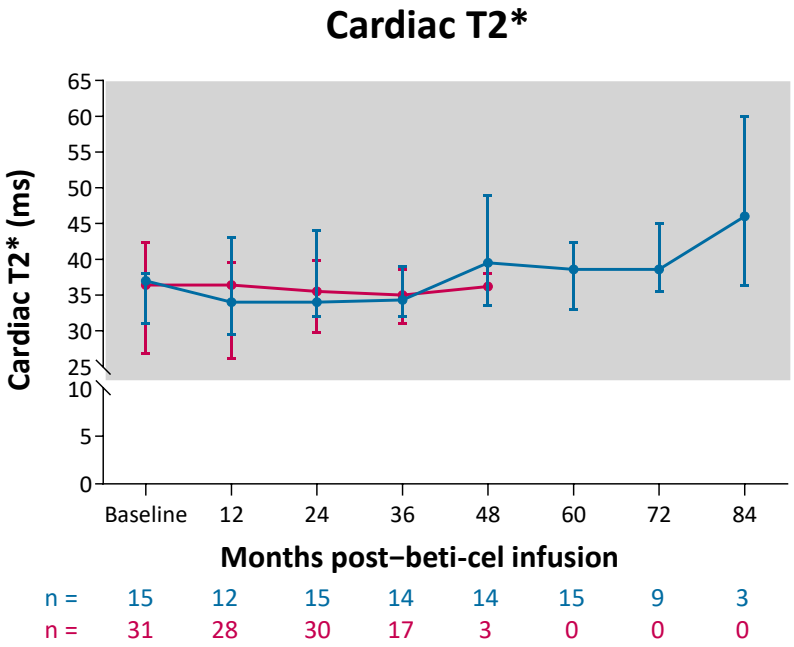


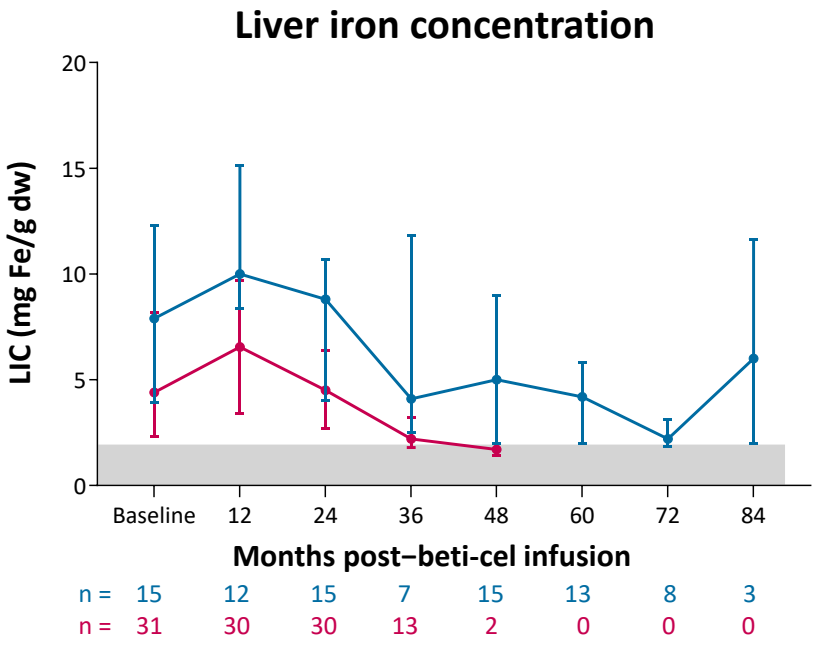
n =	27	27	27	9	0	0

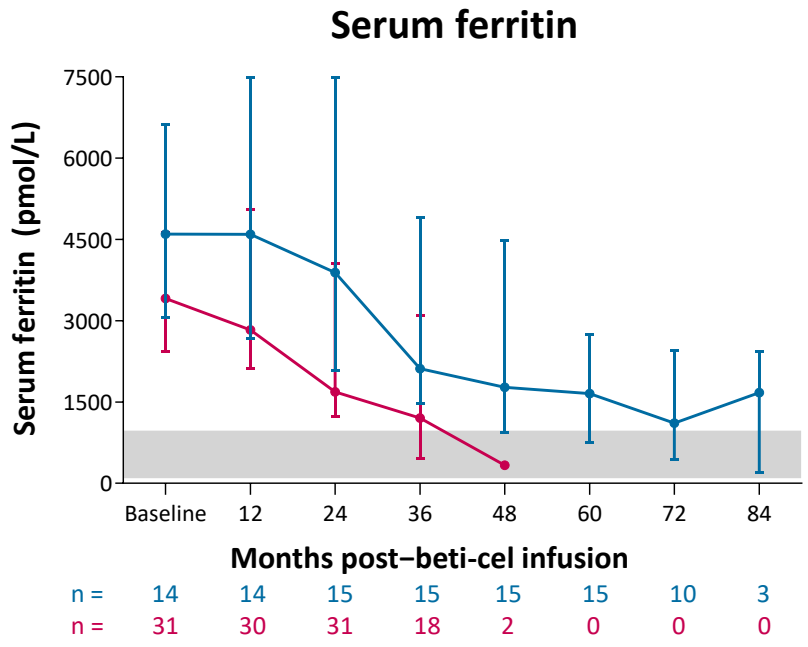
*Erythropoietin data were not collected in phase 1/2 studies.
Median (Q1, Q3) depicted. Grey bars indicate normal range.

sTfR, soluble transferrin receptor.

Reductions in iron burden in patients who achieved TI







Phase 1/2 Phase 3

Correlation† of serum ferritin vs LIC

Month 24: 0.639, $P < 0.0001$ (n = 45)

Month 36: 0.928, $P < 0.0001$ (n = 20)

Month 48: 0.596, $P = 0.0115$ (n = 17)

†Correlations shown as Pearson correlation coefficient, *P* value.
Median (Q1, Q3) depicted. Last-observation-carried-forward imputed values are included.

LIC, liver iron concentration; TI, transfusion independence.

Iron management in patients who achieved TI

- **74% (34/46) restarted iron chelation after beti-cel infusion**
  - Time to starting chelation after beti-cel infusion was 8.1 (0.8 – 25) months and total unsupported Hb at study last visit ranged from 8.5 – 14.9 g/dL for these 34 patients
  - 20/34 patients who restarted iron chelation have since stopped
    - Duration of chelation was 25.7 (4.8 – 62.3) months for these 20 patients

- **24% (11/46) of patients received phlebotomy for iron removal, including 5 patients who were receiving iron chelation**
  - ***6 patients received only phlebotomy***
  - Time to starting phlebotomy after beti-cel infusion was 10.8 (3.2 – 31.6) months and total unsupported Hb at study last visit ranged from 10.5 – 14 g/dL for these 11 patients
  - Duration of phlebotomy was 10.4 (2.5 – 66.8) months for 9/11 patients who received phlebotomy; 2/11 patients received 1 phlebotomy procedure post–beti-cel infusion*
  - ***Patients received 6 (1 – 45) phlebotomy procedures post–beti-cel infusion***

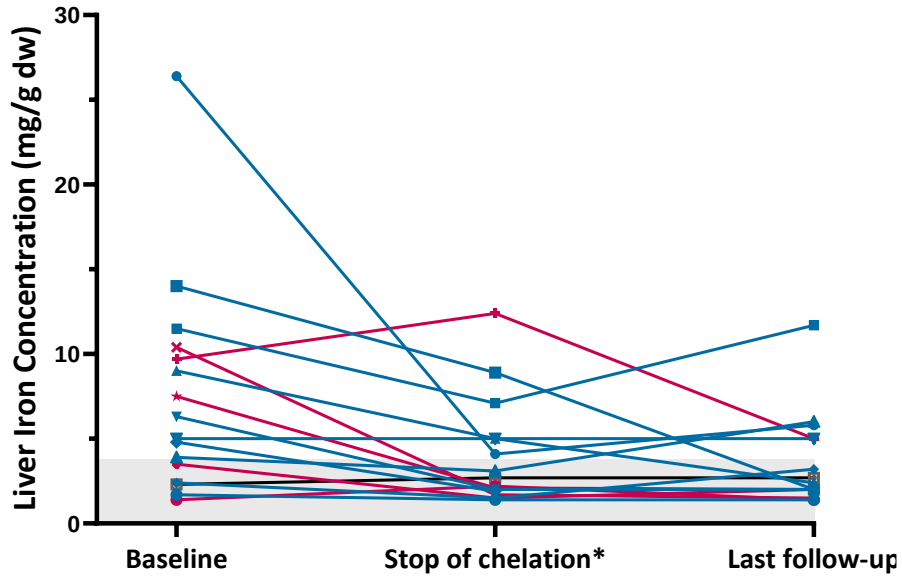
Patients received iron removal therapy at the discretion of the investigator, and decisions to discontinue chelation were made by both the patient and treating physician and were not done because of a target LIC.
Two patients enrolled in phase 3 studies 15% (6/46) of patients never restarted iron management (chelation or phlebotomy).
*The 2/11 patients who received only 1 phlebotomy procedure were not restarted on chelation after beti-cel infusion.
Median (min – max) reported.

TI, transfusion independence.

Chelation and stabilization of iron markers in patients who achieved TI

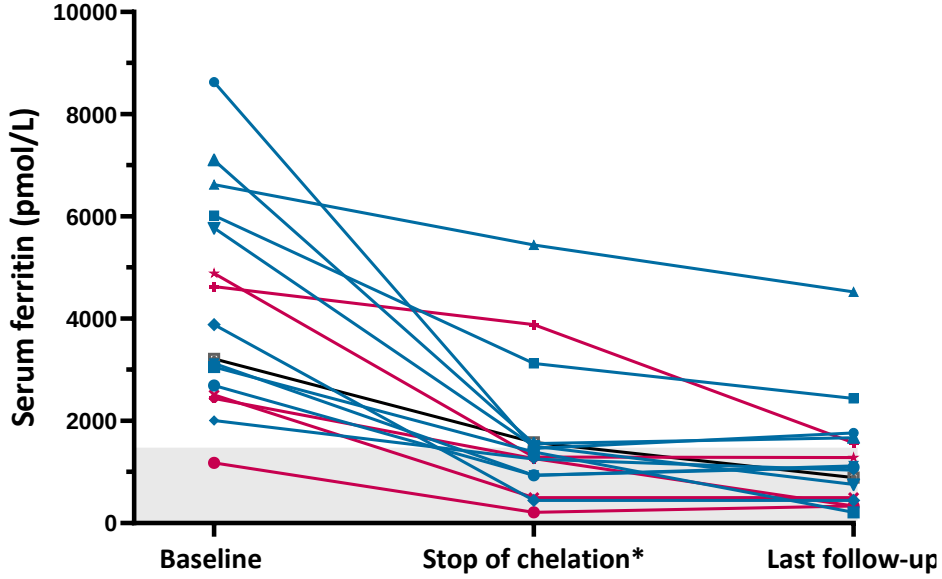
- **Subanalysis showed restoration of iron homeostasis in response to chelation and stabilization of iron markers after chelation was discontinued in patients who achieved TI**

Liver iron concentration for phase 1/2 and 3
TI patients who restarted then stopped iron chelation



	Prior to beti-cel	Time after beti-cel	
Phase 3, n	6	6	6
median follow-up, months (min – max)		12 (12 – 24)	24 (24 – 48)
Phase 1/2, n	10	10	9
median follow-up, months (min – max)		48 (24 – 72)	60 (60 – 84)

Serum ferritin for phase 1/2 and 3
TI patients who restarted then stopped iron chelation



	Prior to beti-cel	Time after beti-cel	
Phase 3, n	6	6	6
median follow-up, months (min – max)		12 (12 – 24)	36 (24 – 48)
Phase 1/2, n	10	10	10
median follow-up, months (min – max)		48 (24 – 72)	72 (60 – 84)

Of the 16 patients included in this subanalysis, 2 patients from phase 1/2 studies were also receiving phlebotomy.
*Iron assessments were completed within approximately ±6 months of stopping chelation.

TI, transfusion independence.

Safety profile of beti-cel in patients in LTF-303

Safety profile after 2 years of follow-up after beti-cel infusion, median 41.49 months (range 23* – 87.5 months)

- All patients are alive at last follow-up
- No vector-derived replication competent lentivirus occurred
- Polyclonal reconstitution; no single clone meets criteria for clonal predominance†
- No insertional oncogenesis and no hematologic malignancies were observed
- Two male patients, one of whom underwent fertility preservation, reported the births of healthy children with their partners

Serious AEs	N = 57‡ *n (%)*
>2 years to last follow-up	
Bacillus bacteremia§	1 (1.8)
Cholelithiasis	1 (1.8)
Diabetic ketoacidosis	1 (1.8)
Ectopic pregnancy	1 (1.8)
Fetal death‖	1 (1.8)
Gallbladder polyp¶	1 (1.8)
Gallbladder wall thickening¶	1 (1.8)
Gonadotropic insufficiency	1 (1.8)
Major depression	1 (1.8)
Neutropenia§	1 (1.8)
Pulmonary embolism	1 (1.8)
Gastritis	1 (1.8)
Placental polyp‖	1 (1.8)

*Patient had their Month 24 visit 23 months post-infusion.
†Criteria for clonal predominance for an individual subject is defined as an insertional site-specific vector copy number > 0.5 c/dg, estimating > 50% clonal contribution.
‡Two patients just enrolled in LTF-303 and do not have additional safety data yet.
§Occurred in the same patient in the context of wild-type HIV infection.
‖ Occurred in the same patient. The case of fetal death was the result of a spontaneous miscarriage.
¶Occurred in the same patient.

AE, adverse event.

Summary of long-term follow-up data from patients treated with beti-cel gene therapy

57 patients from 4 clinical studies evaluating beti-cel for TDT with genotypes spanning a broad range of TDT severity and across several age groups have been enrolled in this 13-year long-term follow-up study to evaluate efficacy and safety

- **One-time beti-cel gene therapy enabled durable TI with up to 7 years of follow-up**
  - Stable expression of gene therapy–derived adult Hb, HbA^{T87Q}
- **Ineffective erythropoiesis and iron overload decreased in patients who achieved TI**
  - Soluble transferrin receptor and erythropoietin demonstrated improvement of ineffective erythropoiesis and reduction in iron overload in patients who achieved TI
  - LIC, serum ferritin, and cardiac T2* improved toward normal levels in patients who achieved TI
  - Subanalysis showed iron reduction in response to chelation and stabilization of iron markers after chelation was discontinued
- **The absence of drug product–related AEs beyond 2 years post-infusion supports a favorable long-term safety profile of beti-cel**
  - No vector-derived replication-competent lentivirus or events of insertional oncogenesis or hematologic malignancy have been reported

beti-cel is a potentially curative gene therapy for patients with TDT through the durable achievement of TI and normal or near-normal Hb levels

AE, adverse event; Hb, hemoglobin; LIC, liver iron concentration; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence.

Data as of August 18, 2021

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