Long-Term Efficacy and Safety of Betibeglogene Autotemcel (beti-cel) Gene Therapy for the Treatment of Transfusion-Dependent β-Thalassemia: Results in Patients with up to 6 Years of Follow-up

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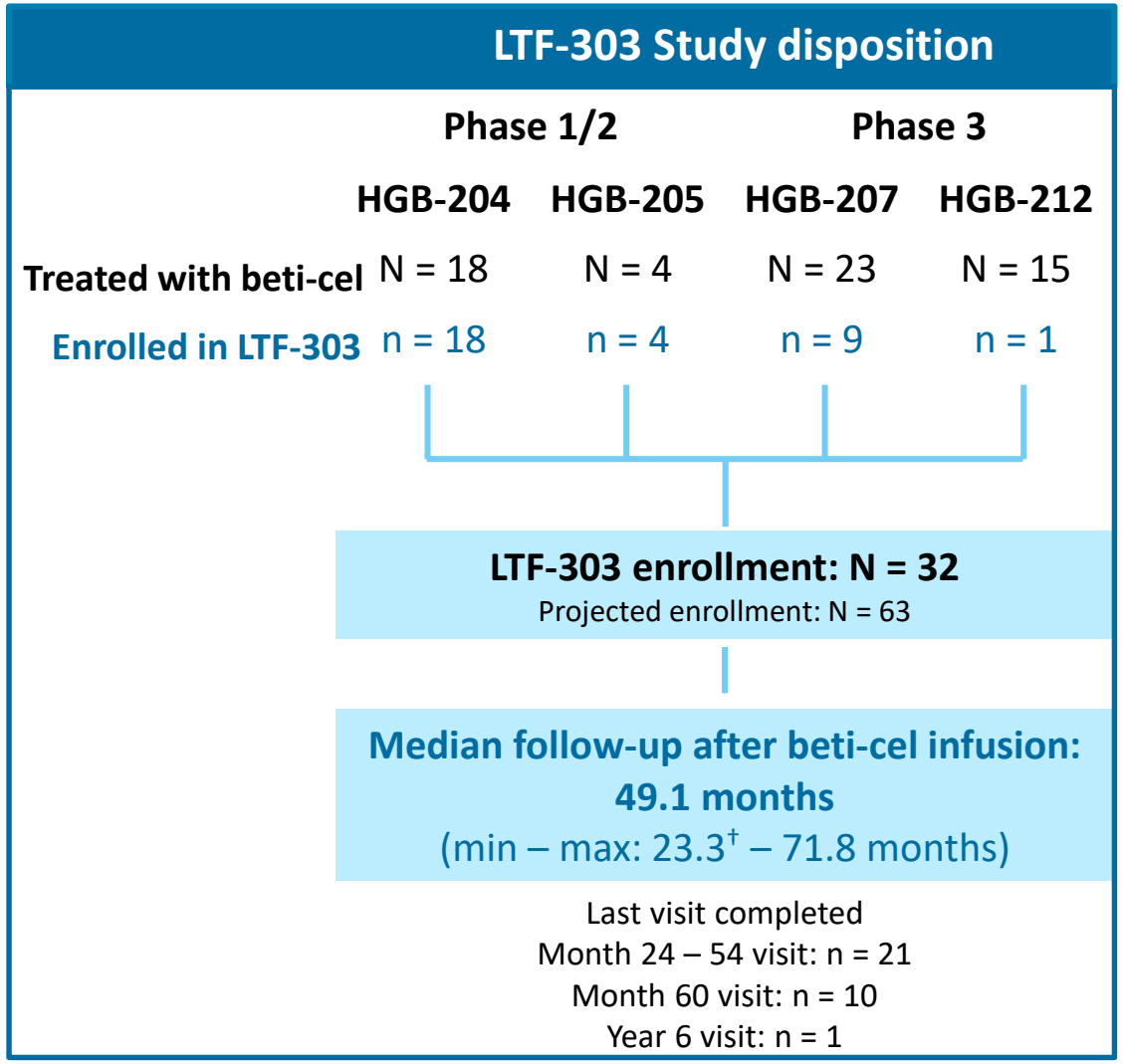
Betibeglogene autotemcel (beti-cel) LTF-303 study overview

- 60 patients with TDT have been treated with beti-cel (LentiGlobin for β-thalassemia) in 4 clinical studies (HGB-204, HGB-205, HGB-207, HGB-212)
  - Lentiviral vector - β-globin gene with T87Q modification
  - Busulfan myeloablative conditioning, IV infusion of beti-cel
- After 2-years of follow-up, patients are invited to enroll in a 13-year, long-term follow-up study, LTF-303

LTF-303 key endpoints

Assessed every 6 months for 3 years and then annually

- Efficacy
  - VCN, HbA^{T87Q}, total Hb
  - Transfusion independence*
  - Biomarkers of ineffective erythropoiesis
- Iron burden and use of iron removal therapy
- Safety
  - DP-related AEs and all SAEs
  - Evidence of replication-competent lentivirus and insertional oncogenesis



*Transfusion independence is defined as weighted average Hb ≥ 9 g/dL without pRBC transfusions for ≥ 12 months

†Patient had their Month 24 visit 23.3 months post-infusion

AE, adverse event; Hb, hemoglobin; IV, intravenous; pRBC, packed red blood cell; transfusion-dependent β-thalassemia (TDT); SAE, serious adverse event; VCN, vector copy number.

Patient and drug product characteristics in LTF-303

Patient characteristics at baseline prior to infusion

		Phase 1/2 (N = 22)	Phase 3 (N = 10)
Genotypes, n (%)	β^0/β^0	**8** (36)	**1** (10)
	β^E/β^0	**9** (41)	**3** (30)
	β^+/β^+	**3** (14)	**2** (20)
	β^0/β^+	**1** (4.5)	**4** (40)
	β^0/β^{X*}	**1** (4.5)	**0** (0)
Age at consent prior to infusion, median (min – max), years		**20** (12 – 35)	**20** (12 – 26)
Pre-study pRBC transfusion volume†, median (min – max), mL/kg/yr		**171.2** (124.4 – 273.2)	**179.6** (158.7 – 251.3)
Liver iron concentration, median (min – max), mg Fe/g dw		**7.1** (0.4 – 26.4)	**4.0** (1.0 – 19.6)
Cardiac T2*, median (min – max), msec		**34** (10 – 54)	**37** (26 – 45)

Drug product characteristics (average/patient)
median (min – max)

	Phase 1/2 (N = 22)	Phase 3 (N = 10)
Vector copy number, vector copies/diploid genome	**0.8** (0.3 – 2.1)	**3.2** (2.4 – 4.5)
CD34+ cells transduced, %	**32** (17 – 58)	**82** (53 – 90)
Cell dose, x 10^6 CD34+ cells/kg	**8.9** (5.2 – 18.1)	**7.7** (5.0 – 13.6)

* Unknown allele is an unidentified β^+ allele since patient is producing endogenous HbA.

† Retrospective data 2 yrs prior to enrollment in parent study; Hb, hemoglobin; pRBC, packed red blood cells.

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

Beti-cel-related AEs at any time post-infusion in patients enrolled in LTF-303

- No beti-cel-related AEs beyond 2 years post-infusion
- All beti-cel-related AEs were Grade 1/2

Beti-cel-related AEs	N = 32 n (%)
Day of infusion	
Abdominal pain	3 (9)
Dyspnea	1 (3)
Hot flush	1 (3)
Non-cardiac chest pain	1 (3)
Post-infusion through 2 yrs follow-up	
Erythroid dysplasia*	1 (3)

*Grade 1 mild dysplastic-like changes in the erythroid series in a bone marrow sample were seen at Month 24 compared with a previous aspirate in a patient who continues to receive transfusions. Bone biopsy at Month 30 showed active trilineage hematopoiesis with no dysplasia noted; Month 36 insertion site analysis indicated no clonal dominance

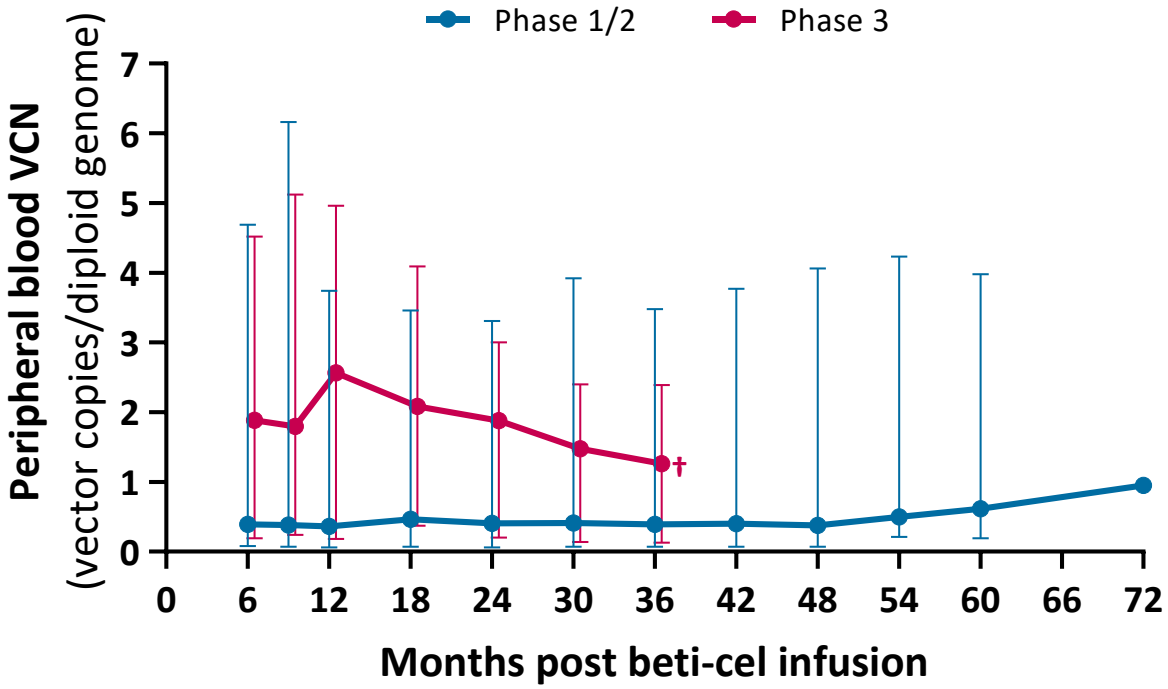
Safety profile after 2 years of follow-up

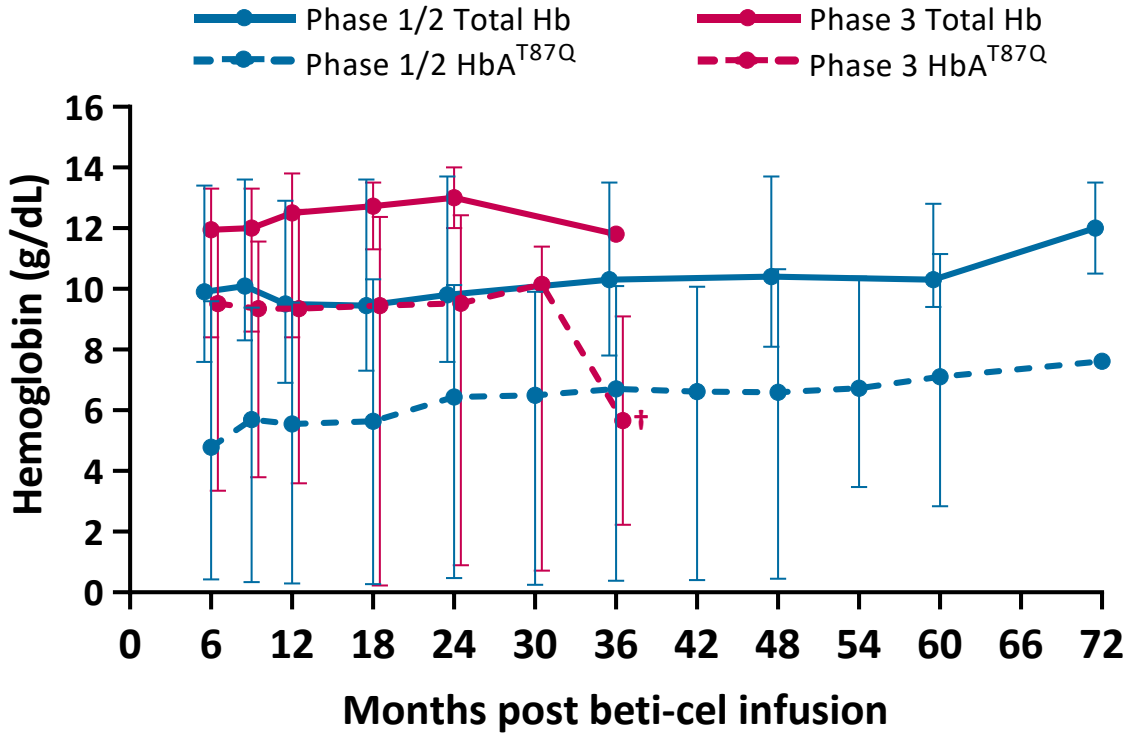
- All patients are alive at last follow-up
- No vector-derived replication competent lentivirus
- Polyclonal reconstitution; no insertional oncogenesis

Serious AEs	N = 31* *n (%)*
>2 years to last follow-up	
Bacillus bacteremia†	1 (3)
Ectopic pregnancy	1 (3)
Gallbladder polyp^	1 (3)
Gallbladder wall thickening^	1 (3)
Gonadotropic insufficiency	1 (3)
Major depression	1 (3)
Neutropenia†	1 (3)

*One patient just enrolled in LTF-303 and does not have additional safety data yet
†Occurred in the same patient
^Occurred in the same patient

Persistent vector-positive cells and durable HbA^{T87Q} support stable total Hb

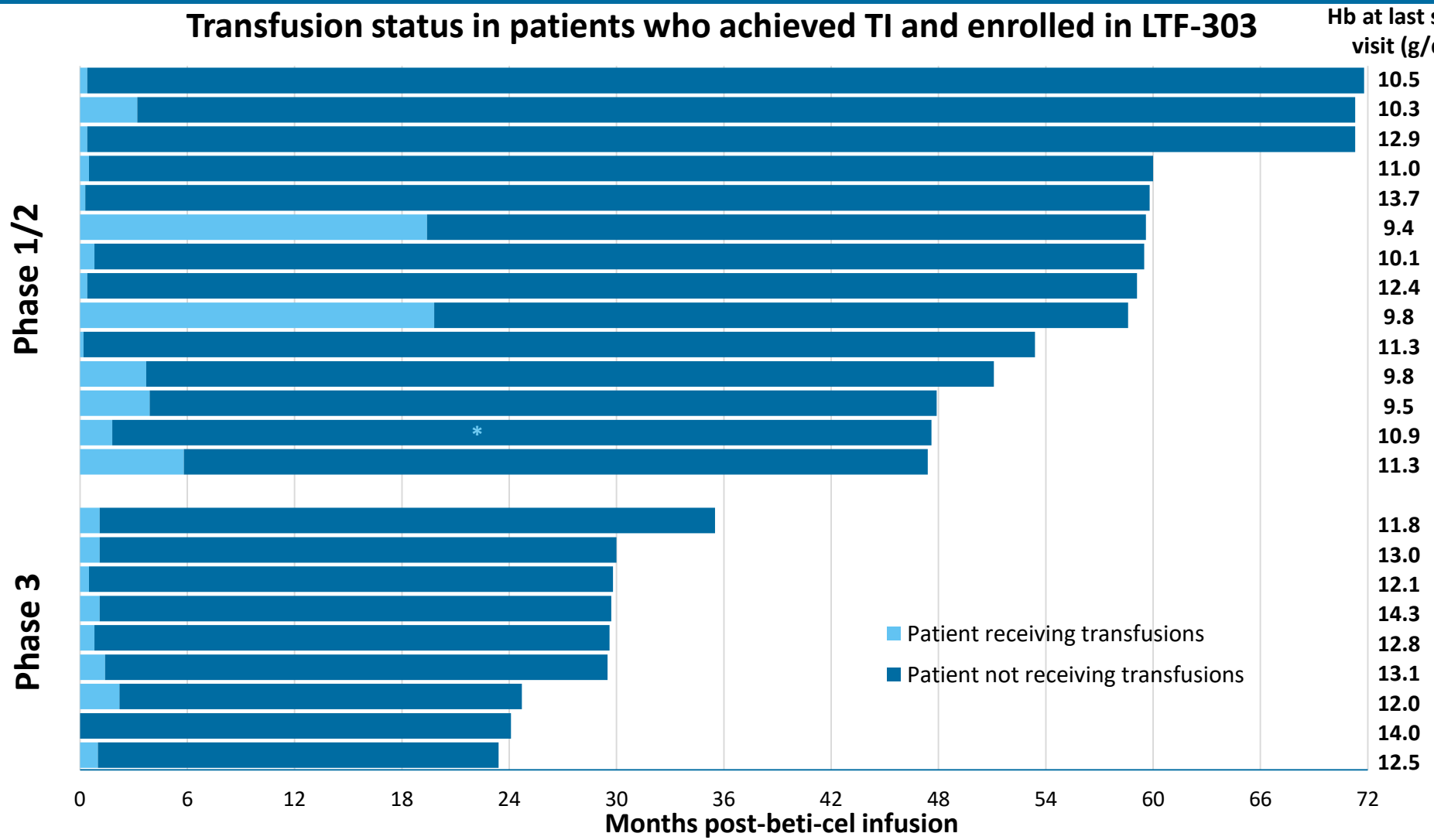




†The change in peripheral blood VCN and HbA^{T87Q} levels in phase 3 at Month 36 are the result of a change in sample size. The 2 patients with Month 36 evaluation had Month 30 and 36 PB VCN levels of 2.39 and 2.39 and 0.14 and 0.13, respectively; HbA^{T87Q} levels at Month 30 and 36 were 9.9 and 9.1 g/dL and 0.7 and 2.2 g/dL, respectively. Median (min – max) depicted.
*number of patients with HbA^{T87Q} evaluation

Hb, hemoglobin; VCN, vector copy number.

Durable transfusion independence is maintained with long term follow-up



64% (14/22) of patients in Phase 1/2 achieved TI†
Duration of ongoing TI:
51.2 (28.1 – 69.4) months

Weighted average Hb:
10.4 (9.4 – 13.3) g/dL

90% (9/10) of patients in Phase 3 achieved TI†
Duration of ongoing TI:
26.1 (19.4 – 31.4) months

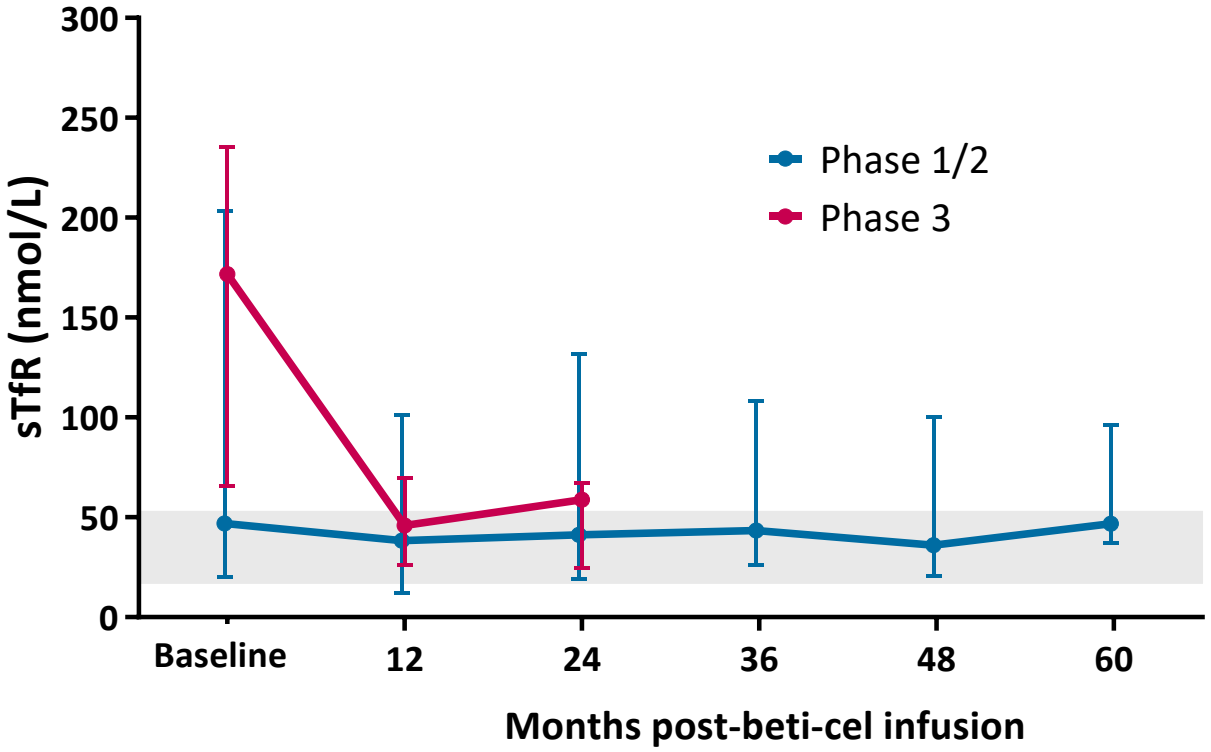
Weighted average Hb:
12.5 (11.9 – 13.5) g/dL

All patients who achieved TI, maintain TI

*Patient had a single transfusion for an acute event of Bartonella infection; †Includes patients of all genotypes/ages who entered LTF-303.
Hb, hemoglobin; TI, transfusion independence (defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months).

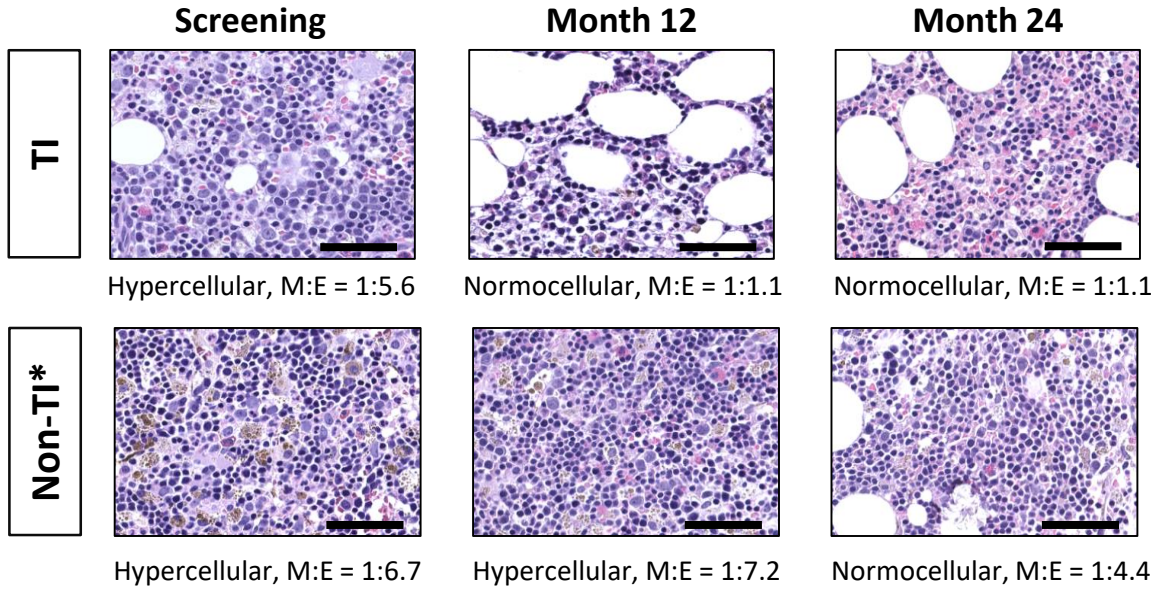
Improved erythropoiesis in transfusion independent patients

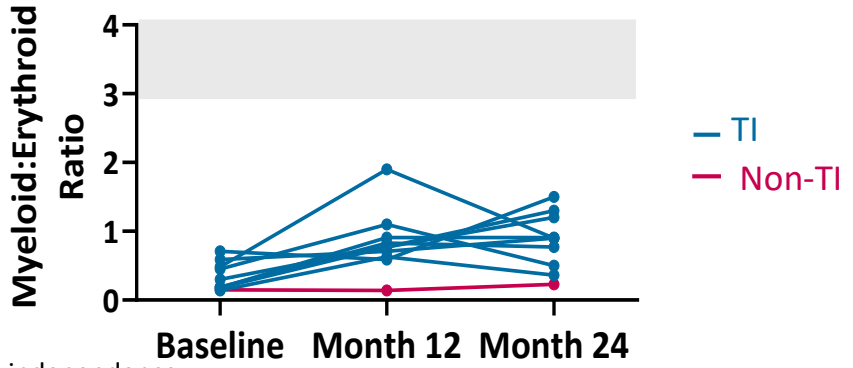
Soluble transferrin receptor (sTfR) in patients who achieved transfusion independence



*This patient did not achieve TI and resumed transfusions 14.5 months post-infusion.

Bone marrow assessment of patients treated in Phase 3 studies and enrolled in LTF-303

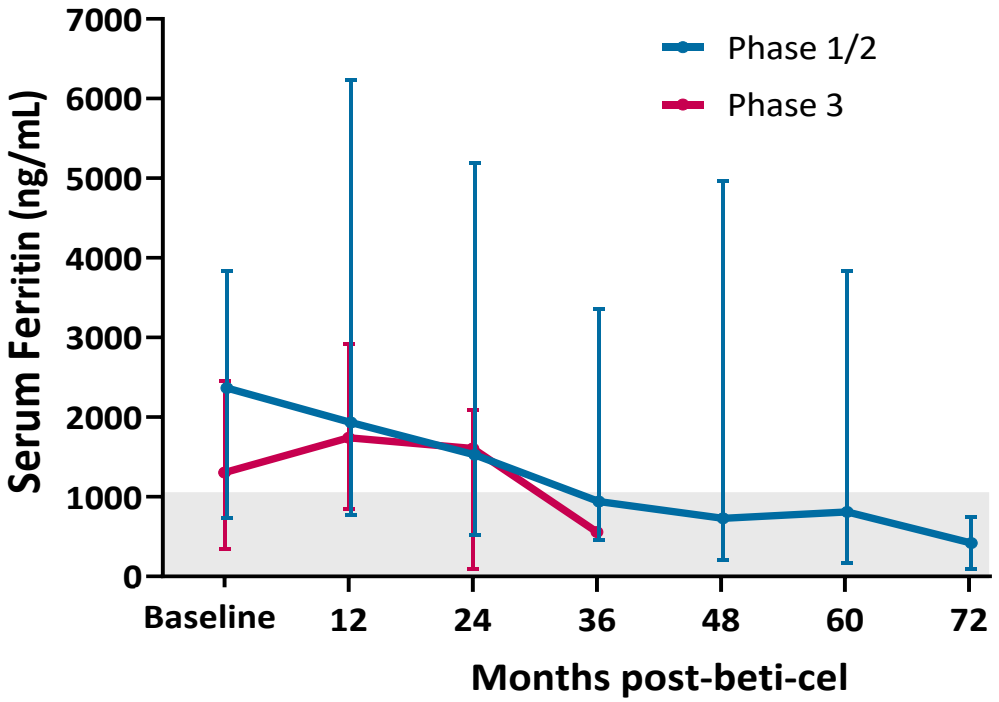




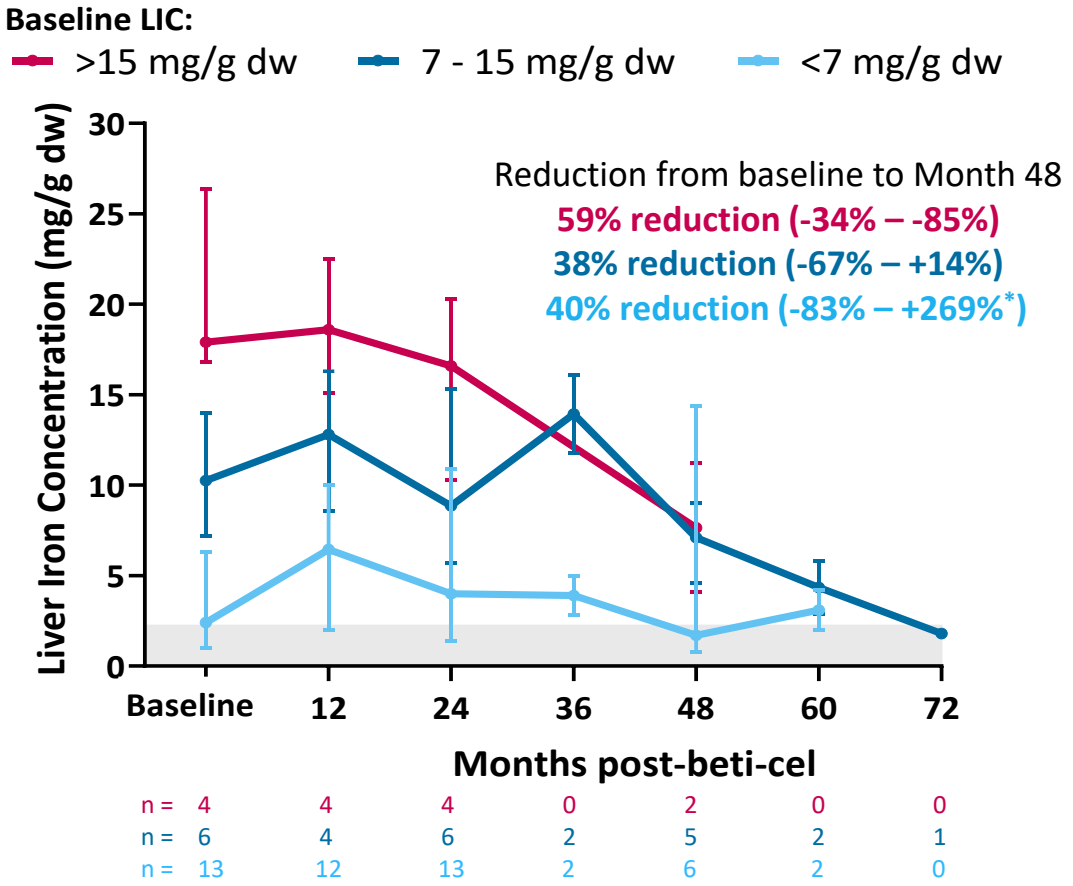
Black bar indicates 50 µm; Gray bar indicates reference range (Origa R. GeneReviews®. 2018); M:E, myeloid:erythroid; TI, transfusion independence.

Reduced iron burden over time in transfusion independent patients

Serum ferritin in patients who achieved TI



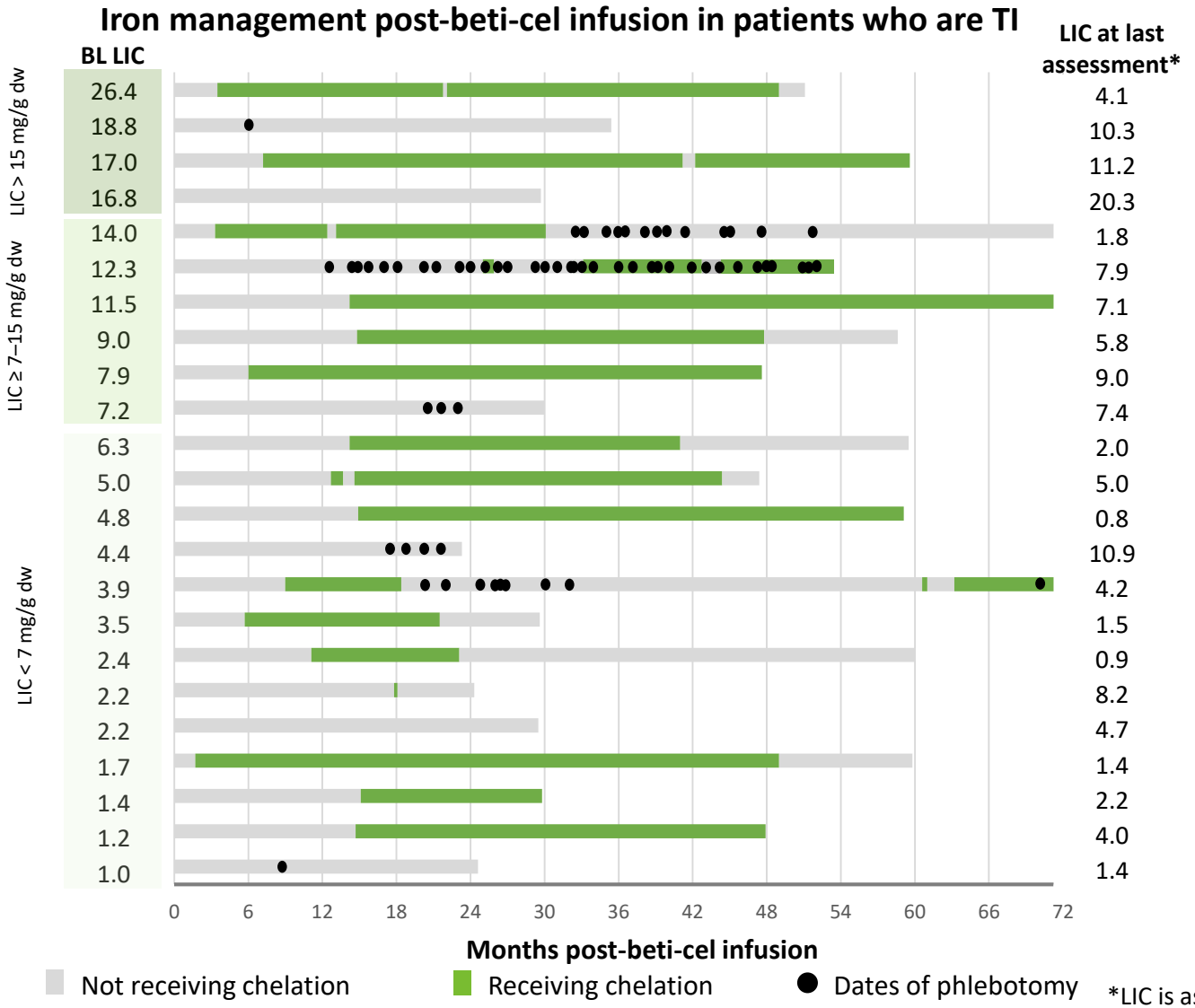
Liver iron concentration in patients who achieved TI



- Cardiac T2* remains stable and >20 msec at last assessment

*The patient with a 269% increase at Month 48 had an LIC over time of 3.9 mg/g dw (baseline), 3.6 mg/g dw (Month 24), 2.8 mg/g dw (Month 36), 14.4 mg/g dw (Month 48), 4.2 mg/g dw (Month 60).
Median (min – max) depicted. Gray bar indicates reference range. LIC, liver iron concentration; TI, transfusion independence.

Most patients who achieved TI have been able to stop chelation



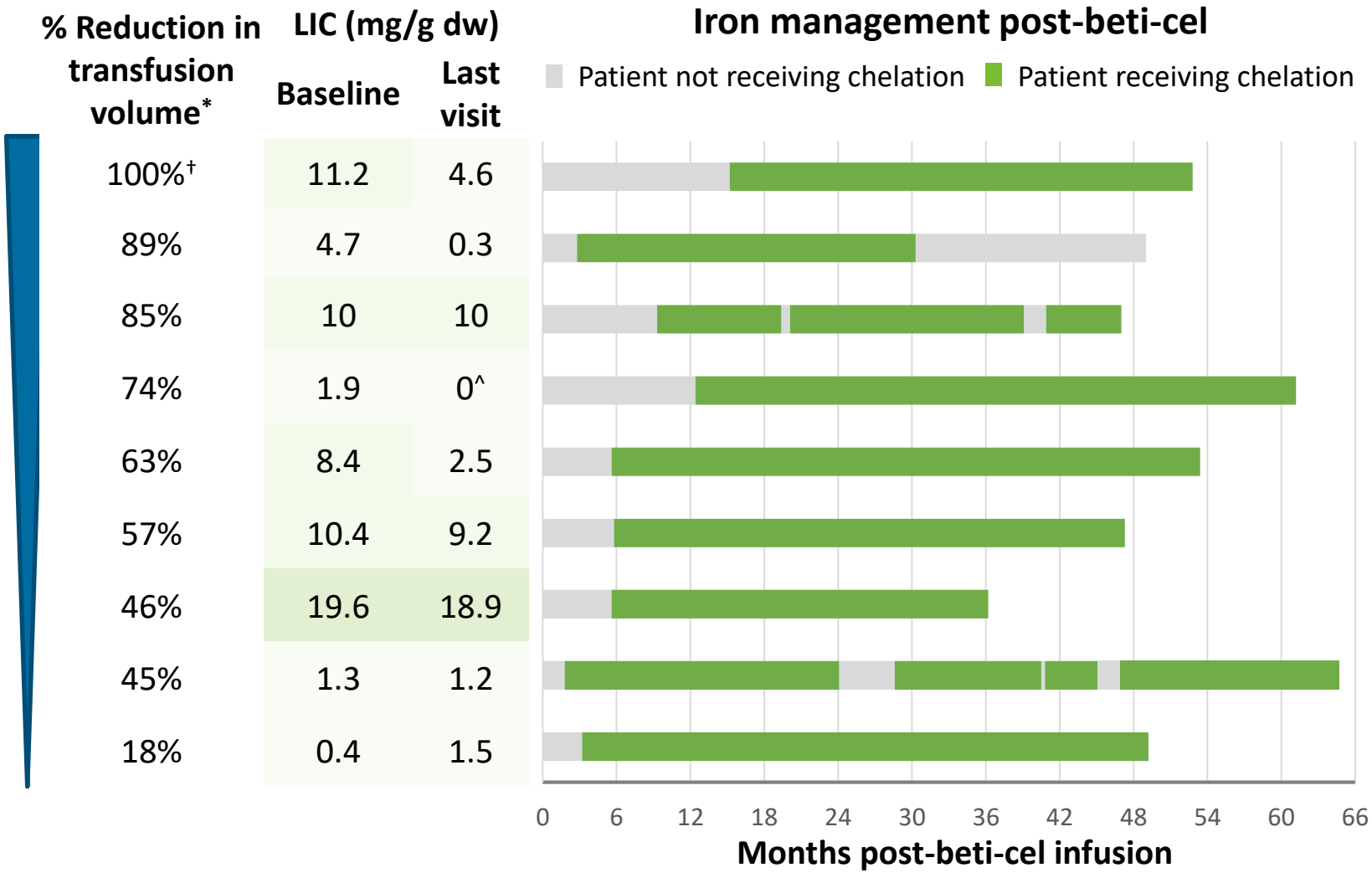
- **74% (17/23) restarted iron chelation a median of 12.7 (1.7 – 25.0) months after beti-cel infusion**
  - Median duration of chelation use was 33.0 (0.1 – 62.3) months
  - **53% (9/17) of patients who restarted iron chelation have since stopped**
- **30% (7/23) of patients received phlebotomy** for iron removal including 3 patients who were receiving iron chelation
  - Total unsupported Hb at study last visit in these patients ranged from 10.5 – 13.0 g/dL

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 due to a target LIC.

*LIC is assessed every 12 months. BL, baseline; LIC, liver iron concentration; TI, transfusion independence.

LIC remained stable or decreased in most patients who did not achieve TI

% Reduction in transfusion volume*	LIC (mg/g dw) Baseline	LIC (mg/g dw) Last visit
100%†	11.2	4.6
89%	4.7	0.3
85%	10	10
74%	1.9	0^
63%	8.4	2.5
57%	10.4	9.2
46%	19.6	18.9
45%	1.3	1.2
18%	0.4	1.5



- All 9 patients who did not achieve TI resumed iron chelation
  - One of these patients has not received iron chelation in 19 months

LIC > 15 mg/g dw
LIC ≥ 7–15 mg/g dw
LIC < 7 mg/g dw

*Reduction in annualized transfusion volume from month 6 through last follow-up; †Patient has stopped transfusions for >49 months, but has Hb < 9 therefore does not meet the definition of transfusion independence.
^Value was below the limit of quantification. LIC, liver iron concentration; TI, transfusion independence

Summary of patients treated with beti-cel gene therapy and enrolled in long-term follow-up study, LTF-303

With up to 6 years of follow-up, one-time beti-cel gene therapy enabled durable transfusion independence in the majority of patients

- Persistent vector-positive hematopoietic cells and stable gene therapy-derived adult Hb, HbA^{T87Q}, support durable TI

Ineffective erythropoiesis and iron overload improved in patients who achieved transfusion independence

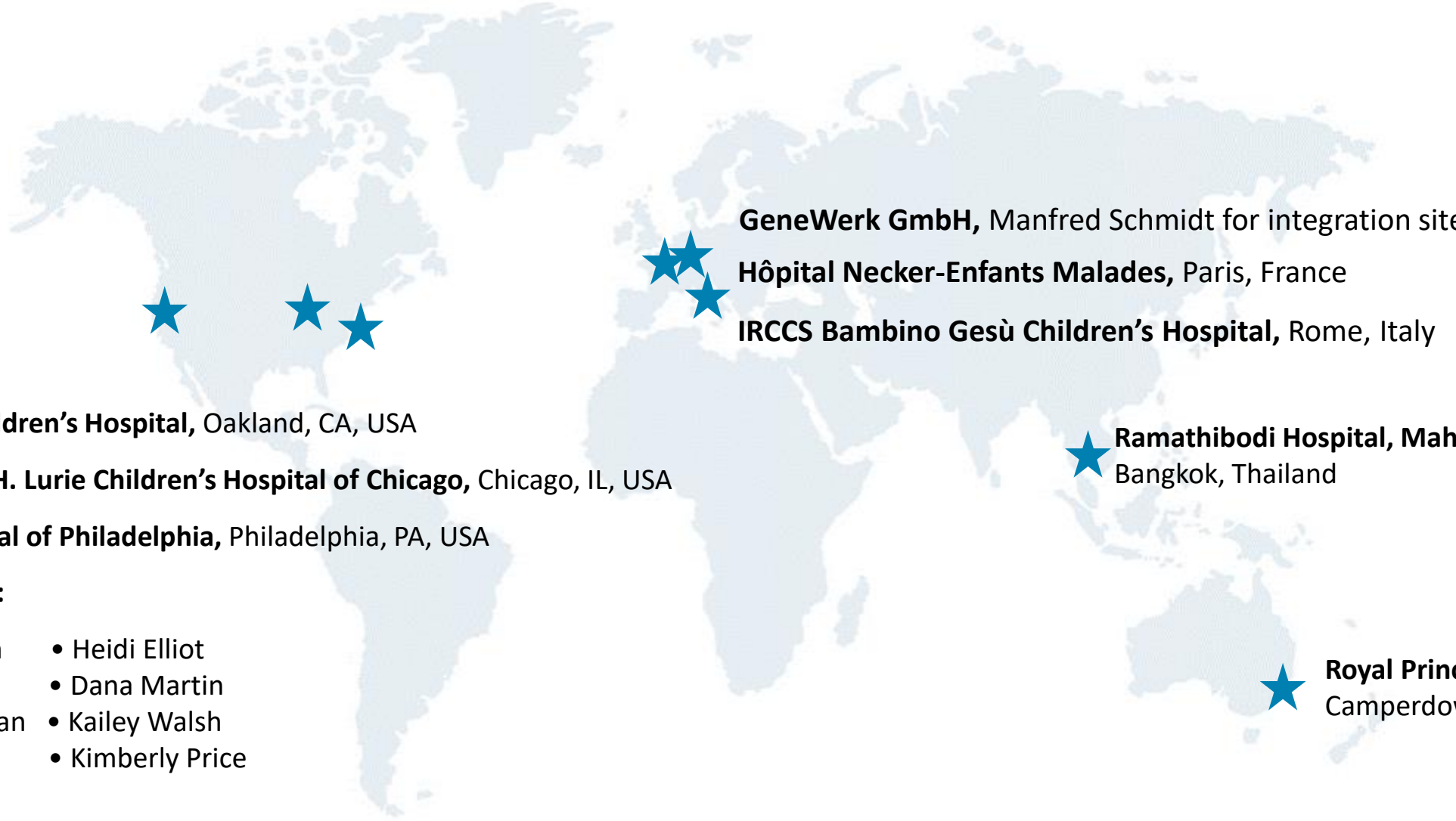
- Serum and histologic biomarkers demonstrate improvement of ineffective erythropoiesis in patients who achieve TI
- 53% (9/17) of patients who achieved TI and restarted iron chelation have since stopped chelation and 7/23 patients who achieved TI received phlebotomy
- Reductions in LIC of 59% and 38% in patients with baseline LIC of > 15 mg/g dw and LIC ≥ 7 – 15 mg/g dw, respectively, at Month 48

The absence of drug product-related adverse events beyond 2 years post-infusion supports favorable the long-term safety profile of beti-cel

- All patients are alive at last follow-up
- No vector-derived replication-competent lentivirus nor events of insertional oncogenesis have been reported

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

Thank you to the study participants and their families



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