Favorable outcomes in pediatric patients in the phase 3 HGB-207 (Northstar-2) and HGB-212 (Northstar-3) studies of betibeglogene autotemcel gene therapy for the treatment of transfusion-dependent β-thalassemia

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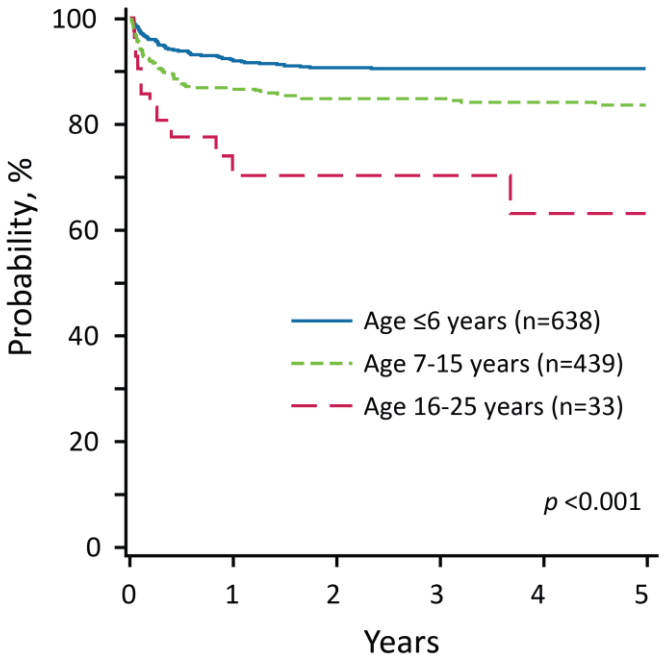
Betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy

- Allo-HSCT is a potentially curative option for β-thalassemia with best outcomes observed in young patients
  - Limitations include lack of donor availability, risk of graft failure, GVHD, and mortality[1]
- Beti-cel aims to establish lifelong, functional adult Hb allowing for the achievement of transfusion independence without the need for a donor
- In phase 3 studies, 83% (10/12) of adult patients with TDT treated with beti-cel achieved transfusion independence
  - These results supported expansion to include adolescent and younger patients

Overall survival by age at allo-HSCT (N = 1110)[1]



1. Li C et al. *Blood Adv*. 2019; 3(17):2562-70.

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; GVHD, graft-versus-host-disease; Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia

Transfusion independence is defined as weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months

Study design of ongoing phase 3 studies HGB-207 and HGB-212

Key eligibility criteria

- ≤50 years of age with TDT*
- HGB-207: non-β^0/β^0 genotypes
- HGB-212: β^0/β^0, $\beta^0/\beta^{+\text{ IVS-I-110}}$ and $\beta^{+\text{ IVS-1-110}}/\beta^{+\text{ IVS-1-110}}$

Primary endpoint

HGB-207: Transfusion independence (TI)

- Weighted average Hb ≥ 9 g/dL without pRBC transfusions for ≥ 12 months

HGB-212: Transfusion reduction (TR)

- ≥60% reduction in volume of pRBC transfusions from 12 to 24 months compared to the annualized pRBC transfusion requirement in the 2 yrs prior to enrollment

Key secondary and exploratory endpoints

- TI and TR characteristics
- Hemoglobin assessments
- Ineffective erythropoiesis assessments

Patients aged < 18 yrs at consent treated with beti-cel

HGB-207: n=14
< 12 yrs: n=8
≥ 12 to <18 yrs: n=6

HGB-212: n=10
< 12 yrs: n=5
≥ 12 to < 18 yrs: n=5

Total enrollment: N=24
< 12 yrs: n=13
≥ 12 to < 18 yrs: n=11

Median follow-up after beti-cel infusion
15.5 months
(min – max: 1.1 – 29.5)

*TDT, transfusion-dependent β-thalassemia defined as receiving of ≥100 mL/kg/year pRBCs transfusions or ≥8 episodes/yr in the 2 years preceding enrollment. HGB-207 (NCT02906202), HGB-212 (NCT03207009)

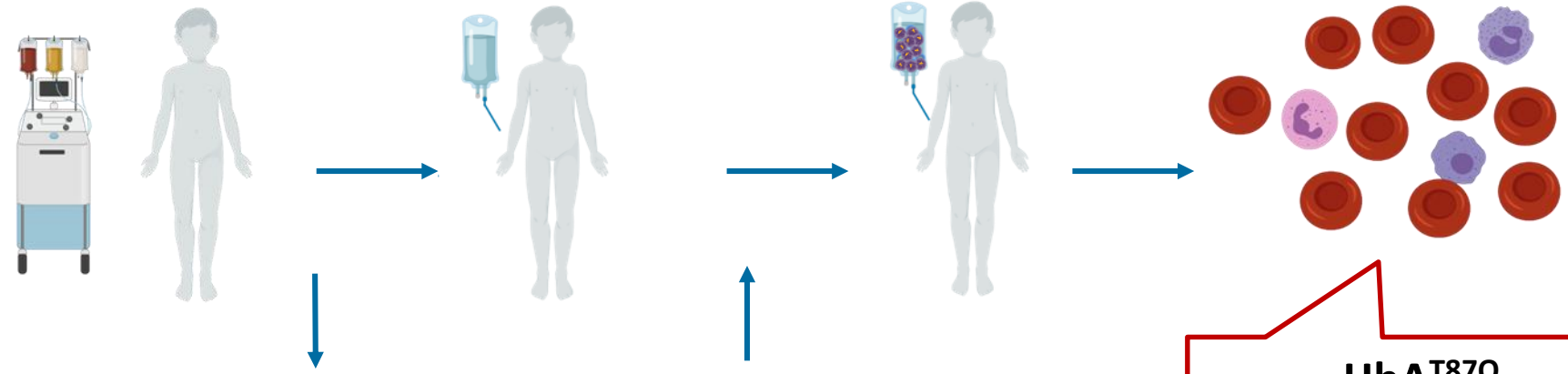
Treatment procedure in the phase 3 studies

Mobilization and HSC collection
(G-CSF + plerixafor) and apheresis

Busulfan myeloablative conditioning

beti-cel IV infusion

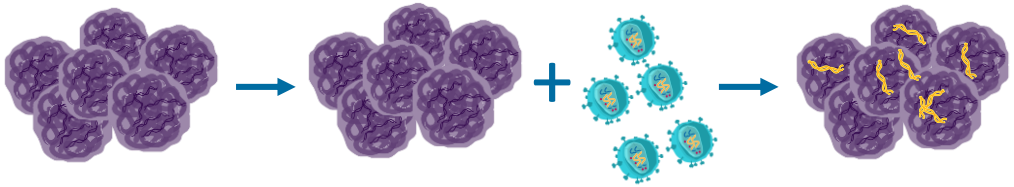
Transduced HSCs engraft and reconstitute RBCs that produce HbA^{T87Q}



2-year follow-up

LTF-303
13-year long-term follow-up study
(15-year total follow-up)

beti-cel centralized manufacturing



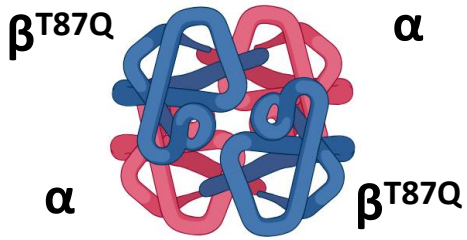
Select CD34+ cells

HSCs transduced with BB305 lentiviral vector (encodes for β$^{A\text{-}T87Q}$-globin)

Cryopreserve, test, release beti-cel drug product

HbA^{T87Q}

- Gene-therapy derived functional adult Hb
- Measurable by HPLC



G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HPLC, high-performance liquid chromatography; HSC, hematopoietic stem cell; IV, intravenous; RBC, red blood cell.

Pediatric patient characteristics

Patient baseline characteristics

		< 12 yrs N = 13	≥ 12 – <18 yrs N = 11
Gender, n (%)	Male	**6** (46)	**7** (64)
	Female	**7** (54)	**4** (34)
Age at assent, median (min – max), yrs		**8** (4 – 11)	**15** (12 – 17)
Liver iron concentration, median (min – max), mg Fe/g dw		**3.8** (1.2 – 12.7)	**5.6** (1 – 13.2)
Cardiac T2*, median (min – max), msec		**38** (15 – 57)	**39** (25 – 75)

Thalassemia medical history

		<12 yrs N = 13	≥12 – <18 yrs N = 11
Genotypes, n (%)	β^0/β^+	**8** (62)	**3** (27)
	β^0/β^0	**3** (23)	**4** (36)
	β^+/β^+	**1** (8)	**4** (36)
	β^E/β^0	**1** (8)	0
Splenectomy, n (%)		**1** (8)	0
Age at first transfusion, median (min – max)		**11 months** (3 months – 3 yrs)	**8 months** (3 months – 11 yrs)

Drug product, conditioning, and engraftment characteristics

	<12 yrs N = 13	≥12 – <18 yrs N = 11
	median (min – max)	
Drug product (average/patient)		
Vector copy number, vector copies/diploid genome	**2.6** (1.9 – 4.7)	**3.3** (1.2 – 6.0)
CD34+ cells transduced, %	**70** (34 – 85)	**82** (34 – 90)
Cell dose, CD34+ cells x 10^6/kg	**9.9** (6.1 – 19.9)	**7.4** (5.0 – 19.4)
Conditioning		
Estimated daily average AUC over 4 days, µM*min	**4164** (3844 – 7497)	**4471** (3708 – 8947)
Dosing frequency, n (%) Q6H	**6** (46)	**8** (73)
Dosing frequency, n (%) Q24H	**7** (54)	**3** (27)
Engraftment		
Neutrophil engraftment, ANC ≥ 500 cells/µL x 3 days, days	**26** (17 – 36)	**26** (16 – 38)
Platelet engraftment, ≥ 20,000 platelets/µL x 3 days, days	**50** (20 – 94)†	**50.5** (25 – 84)^

Target busulfan AUC: q24h: 4200 (min – max: 3800 – 4500) µM*min; q6h: 1050 (min – max: 950 – 1125) µM*min

†2 patients with 1-3 months of follow-up had not yet achieved platelet engraftment as of the datacut.

^1 patient with 1 month of follow-up had not yet achieved platelet engraftment as of the datacut.

ANC, absolute neutrophil counts; AUC, area under the curve; Q6H, every 6 hours; Q24H, every 24 hours.

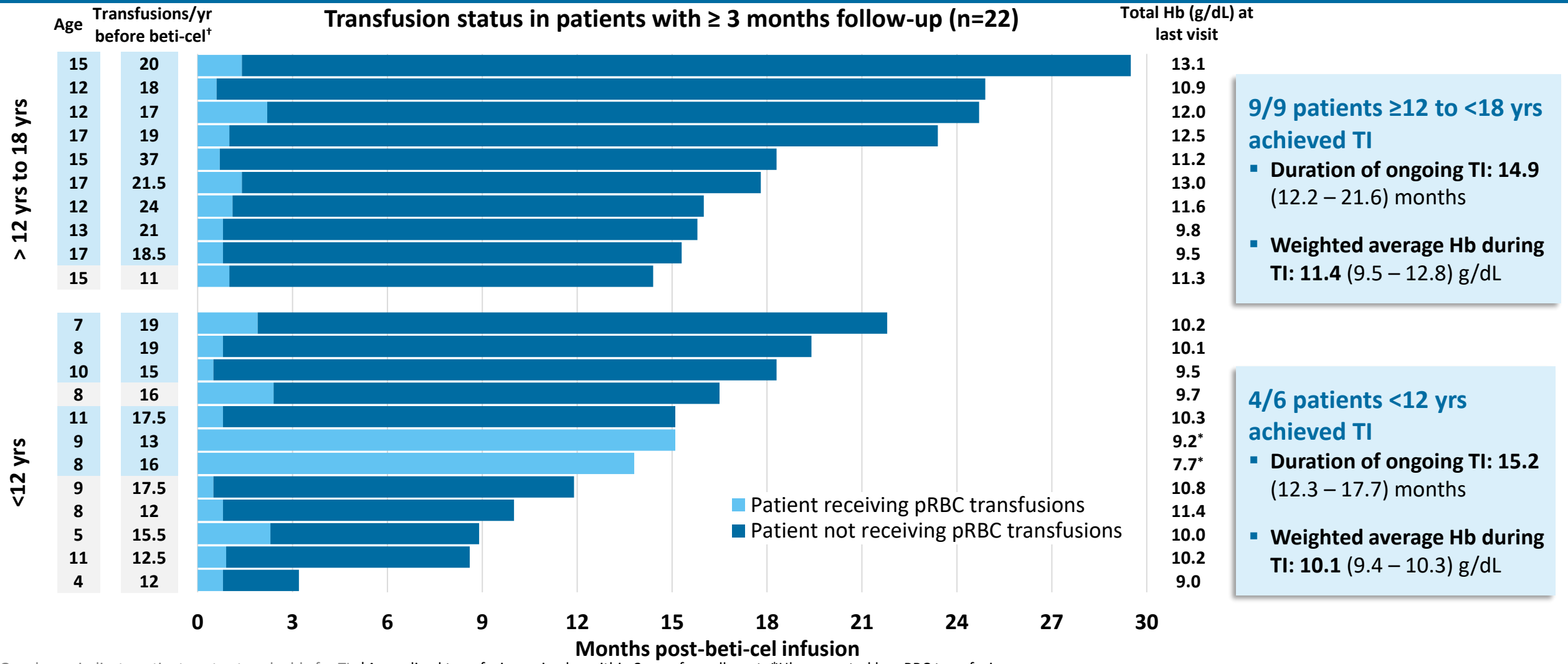
Safety summary of beti-cel in pediatric patients

Non-hematologic grade ≥ 3 AEs* *Post beti-cel infusion in ≥ 3 patients*	**N = 24 n (%)**
Stomatitis	14 (58)
Febrile neutropenia	12 (50)
Decreased appetite	5 (21)
Epistaxis	4 (17)
Alanine aminotransferase increase	3 (13)
Hypoxia	3 (13)
Pyrexia	3 (13)
Serious AEs *Post beti-cel infusion in ≥ 2 patients*	
Pyrexia	3 (13)
Febrile neutropenia	2 (8)
Neutropenia	2 (8)
Stomatitis	2 (8)
Thrombocytopenia	2 (8)
Veno-occlusive liver disease	2 (8)

*Hematologic AEs commonly observed post-transplantation were excluded.

- AEs considered related or possibly related to the drug product
  - Day of infusion:
    - Tachycardia (n = 1, Grade 1)
    - Abdominal pain (n = 2, Grade 1)
  - Post-infusion:
    - One non-serious Grade 3 event of thrombocytopenia
- Veno-occlusive liver disease occurred in 3 patients; all events resolved with defibrotide
  - 2 serious, Grade 4 events occurred in patients aged 12 yrs old
  - 1 non-serious, Grade 2 event occurred in a 5-yr-old
- No graft failure
- All patients are alive at last follow-up
- No replication-competent lentivirus or insertional oncogenesis

87% (13/15) of evaluable pediatric patients achieved transfusion independence



9/9 patients ≥12 to <18 yrs achieved TI

- **Duration of ongoing TI: 14.9** (12.2 – 21.6) months
- **Weighted average Hb during TI: 11.4** (9.5 – 12.8) g/dL

4/6 patients <12 yrs achieved TI

- **Duration of ongoing TI: 15.2** (12.3 – 17.7) months
- **Weighted average Hb during TI: 10.1** (9.4 – 10.3) g/dL

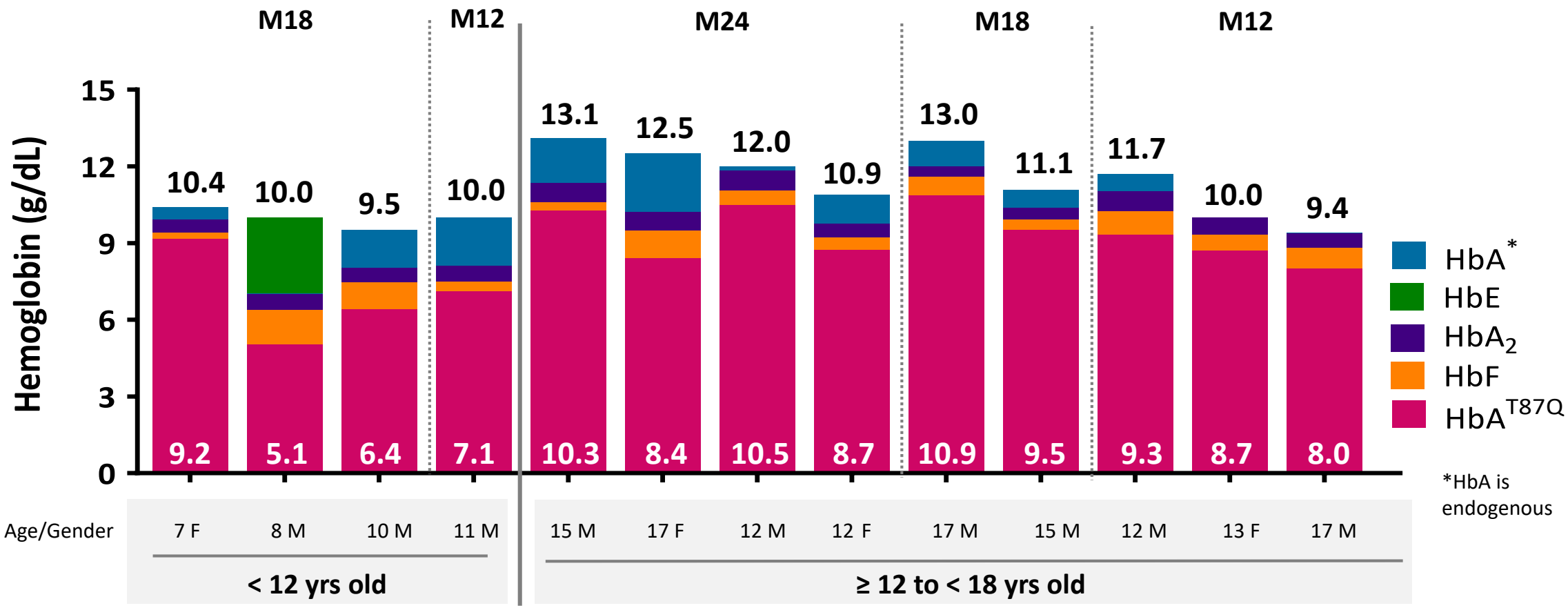
Grey boxes indicate patients not yet evaluable for TI; †Annualized transfusion episodes within 2 yrs of enrollment. *Hb supported by pRBC transfusions

The two patients who continue to receive transfusions received drug product with 61% and 58% vector-positive cells; peripheral blood vector copy number at last study visit was 0.19 copies/diploid genome (c/dg) and 0.22 c/dg.

TI, transfusion independence (defined as weighted average hemoglobin (Hb) ≥ 9 g/dL without packed red blood cell (pRBC) transfusions for ≥ 12 months).

Majority of total Hb is comprised of HbA^{T87Q} in pediatric patients who achieved transfusion independence

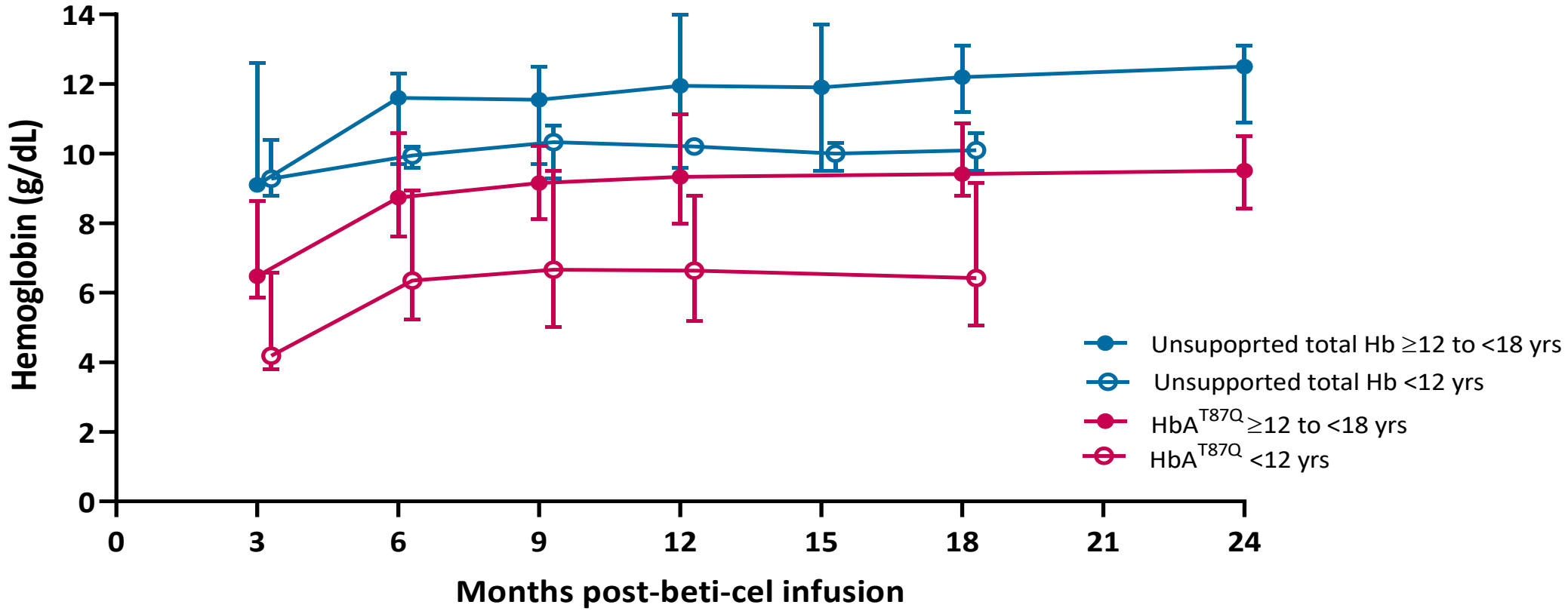
Hb fraction at last assessment in patients who achieved transfusion independence



Hb reference range: Patients < 12 yrs female/male: 11.5 – 16.0 g/dL. Patients ≥ 12 yrs to < 18 yrs female: 12.0 – 15.0 g/dL; male: 12.5 – 16.1 g/dL[1]

Hb, hemoglobin. 1. American College of Clinical Pharmacy. Reference values for common laboratory tests. Pediatric Self-Assessment Program.

Total Hb and HbA^{T87Q} levels stabilize over time in pediatric patients who achieved transfusion independence



≥ 12 to <18 yrs	Total Hb	5	9	9	9	9	6	4
	HbA^{T87Q}	9	9	9	9		6	4
<12 yrs	Total Hb	3	4	4	3	4	3	
	HbA^{T87Q}	4	4	4	4		3	

Unsupported total Hb is defined as total Hb without packed red blood cell transfusion in the preceding ≥ 60 days; Median (min – max) depicted.

Hb reference range: Patients < 12 yrs female/male: 11.5 – 16.0 g/dL. Patients ≥ 12 yrs to < 18 yrs female: 12.0 – 15.0 g/dL; male: 12.5 – 16.1 g/dL[1]

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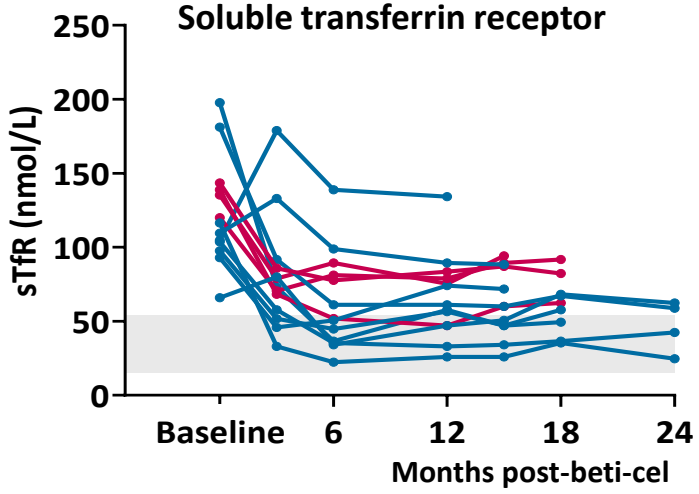
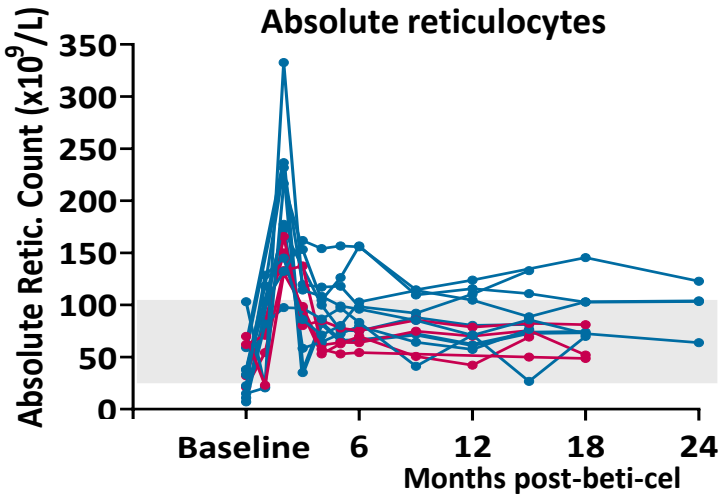
Improvement of ineffective erythropoiesis in pediatric patients who achieved transfusion independence

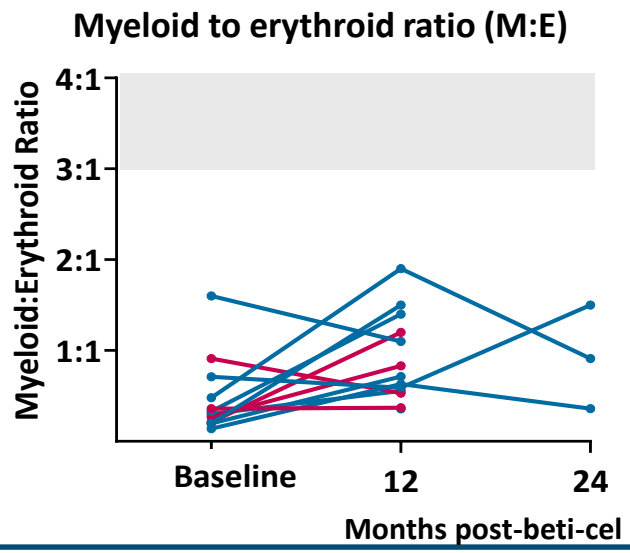
Serum biomarkers



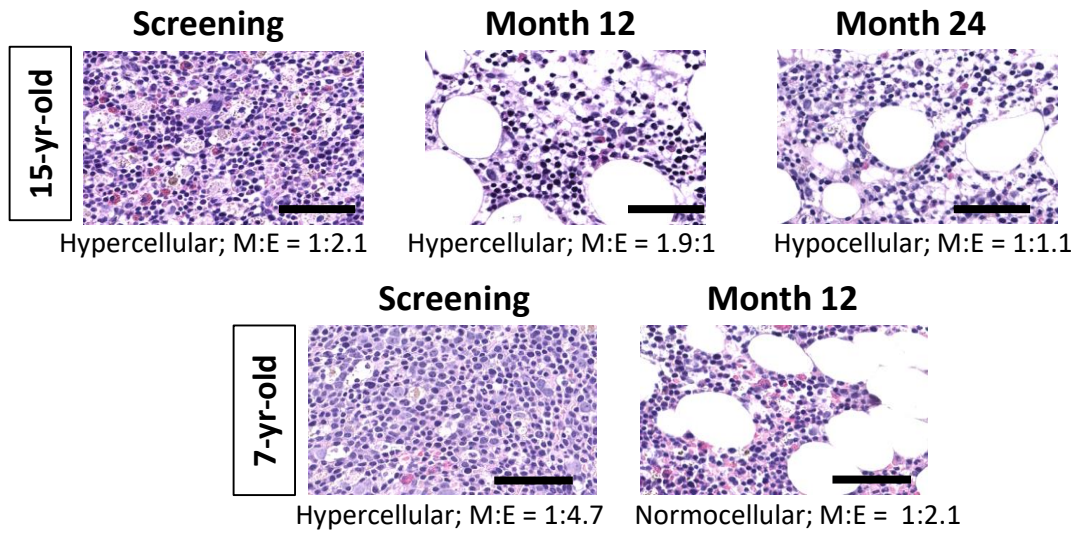


KEY
- ≥12 to <18 yrs
- <12 yrs

Histologic biomarkers



- At Month 12, 75% (9/12) of patients who achieved TI had increased M:E ratio compared to baseline



Gray bars indicate reference range (sTfR reference range is for adult patients); Black bar indicates 50 µm; sTfR, soluble transferrin receptor; TI, transfusion independence.

Phase 3 outcomes in pediatric patients support beti-cel gene therapy as an effective treatment option for patients with TDT across ages

- 87% (13/15) of pediatric patients <18 yrs old achieved durable transfusion independence with median weighted average Hb of 11.3 (9.4 – 12.8) g/dL
  - TI is maintained by gene therapy-derived adult Hb, HbA^{T87Q}
  - Total Hb and HbA^{T87Q} was lower in patients <12 yrs relative to patients ≥12 to <18 yrs
    - Median weighted average Hb during TI was 10.1 g/dL in patients <12 yrs and 11.4 g/dL in patients ≥12 to <18 yrs
  - Pediatric patients achieved TI at a comparable rate to adults in the phase 3 studies (83%)
- Ineffective erythropoiesis improved after beti-cel gene therapy
- The treatment regimen with beti-cel in pediatric patients <18 years old had a safety/tolerability profile dominated by the known effects of myeloablation with single-agent busulfan

Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence (weighted average Hb ≥ 9 g/dL without packed red blood cell transfusions for ≥ 12 months).

Thank you to the study participants and their families

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