2022 aspho CONFERENCE
Advancing Knowledge, Discovery, and Collaboration

betibeglogene Autotemcel in Pediatric Patients with Transfusion-dependent β-thalassemia in Phase 3 Trials

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betibeglogene autotemcel (beti-cel) GT for TDT

- beti-cel is a one-time autologous *ex vivo* GT that aims to establish lifelong, functional HbA allowing for transfusion independence (HbA^{T87Q})[1]
- Phase 3 studies, HGB-207 and HGB-212, demonstrated positive outcomes in adults[1,2]
- Key eligibility criteria include[3,4]:
  - ≤50 years of age, no HLA-identical family donor
  - HGB-207: non-β^0/β^0 genotypes
  - HGB-212: β^0/β^0, $\beta^0/\beta^{+\ IVS\text{-}I\text{-}110}$ and $\beta^{+\ IVS\text{-}1\text{-}110}/\beta^{+\ IVS\text{-}1\text{-}110}$
- Here, we present interim efficacy and safety data in pediatric patients (<18 years) in HGB-207 and -212

Patients aged <18 yrs at consent in phase 3 studies

Mobilization/apheresis complete (N=28)

<12 yrs: n=16	≥12 – <18 yrs: n=12
HGB-207: n=8 HGB-212: n=8	HGB-207: n=6 HGB-212: n=6

beti-cel infused (N=27*)

<12 yrs: n=16	≥12 – <18 yrs: n=11
HGB-207: n=8 HGB-212: n=8	HGB-207: n=6 HGB-212: n=5

Median follow-up after beti-cel infusion: 30.4 months

min – max: 9.0 – 42.9 months

*One patient withdrew consent after mobilization

1. Locatelli et al. *N Engl J Med* 2022;386:415-427; 2. Kwiatkowski et al. *Blood* 2021;138(S1):3085; 3. https://clinicaltrials.gov/ct2/show/NCT02906202 accessed April 19, 2022; 4. https://clinicaltrials.gov/ct2/show/NCT03207009 accessed April 19, 2022.

GT, gene therapy; Hb, hemoglobin; HbA, adult hemoglobin; HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$); HLA, human leukocyte antigen; TDT, transfusion-dependent β-thalassemia; yrs, years.

Data cut-off: August 18, 2021

beti-cel treatment process[1]

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

1 cycle: 86% (24/28)
2 cycles: 14% (4/28)

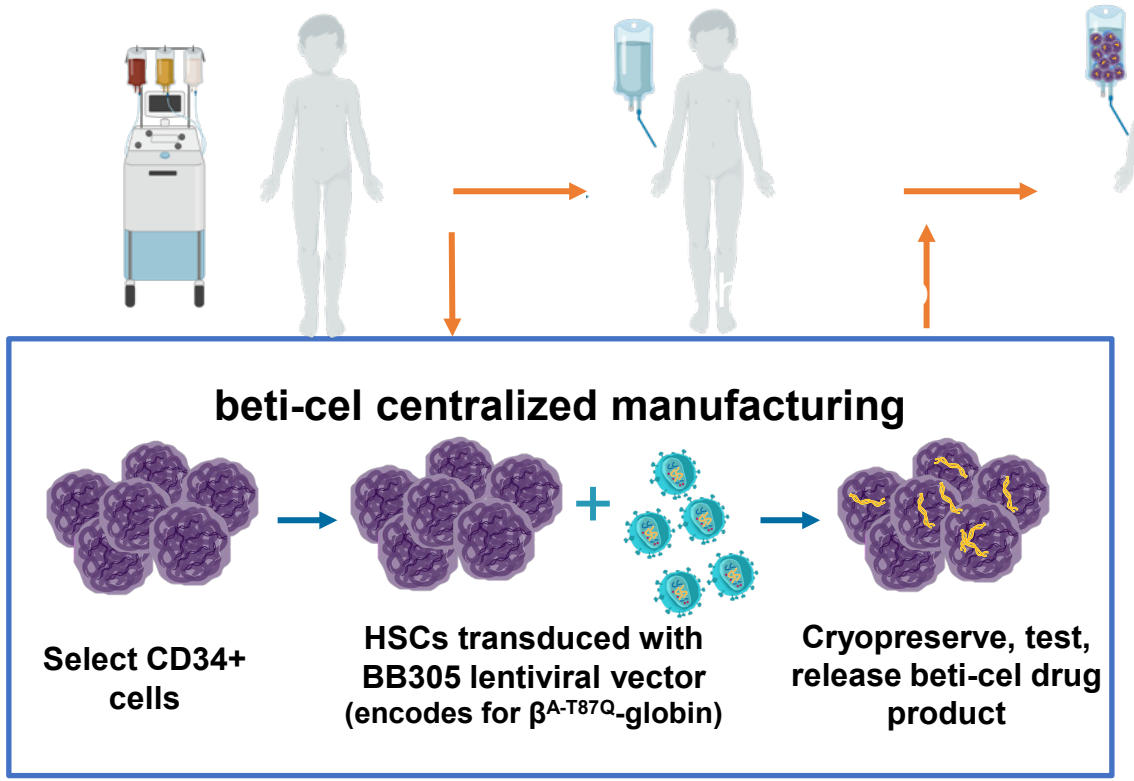
Busulfan myeloablative conditioning

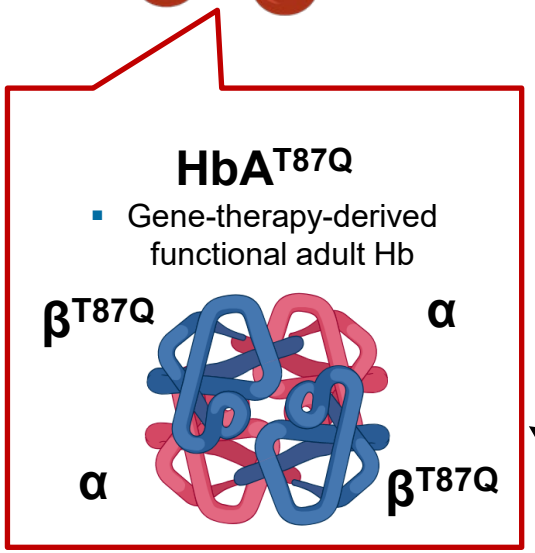
beti-cel IV infusion

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–derived HbA^{T87Q} has oxygen affinity similar to that of endogenous HbA[1]

1. Locatelli et al. *N Engl J Med* 2022;386:415-427.
G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$); HSC, hematopoietic stem cell; IV, intravenous; RBC, red blood cell.

Baseline patient characteristics

		<12 yrs N=16	≥12 – <18 yrs N=11	≥18 yrs N=14
Genotype, n (%)	non-β^0/β^0	**10** (63)	**7** (64)	**12** (86)
	β^0/β^0	**6** (37)	**4** (36)	**2** (14)
Age at assent,[a] median (min – max), yr		**8** (4 – 11)	**15** (12 – 17)	**22.5** (18 – 34)
Liver iron concentration, median (min – max), mg Fe/g dw		**3.0** (1.2 – 12.7)	**5.6** (1.0 – 13.2)	**7.7** (1.4 – 41)
Cardiac T2*, median (min – max), msec		**37** (15 – 57)	**39** (25 – 75)	**36** (17 – 53)
Splenectomy, n (%)		**1** (6.3)	**0**	**6** (43)

[a]For patients <18 years, values represent age at assent. For patients ≥18 years, values represent age at informed consent.
Fe/g dw; iron per gram dry weight.

Data cut-off: August 18, 2021

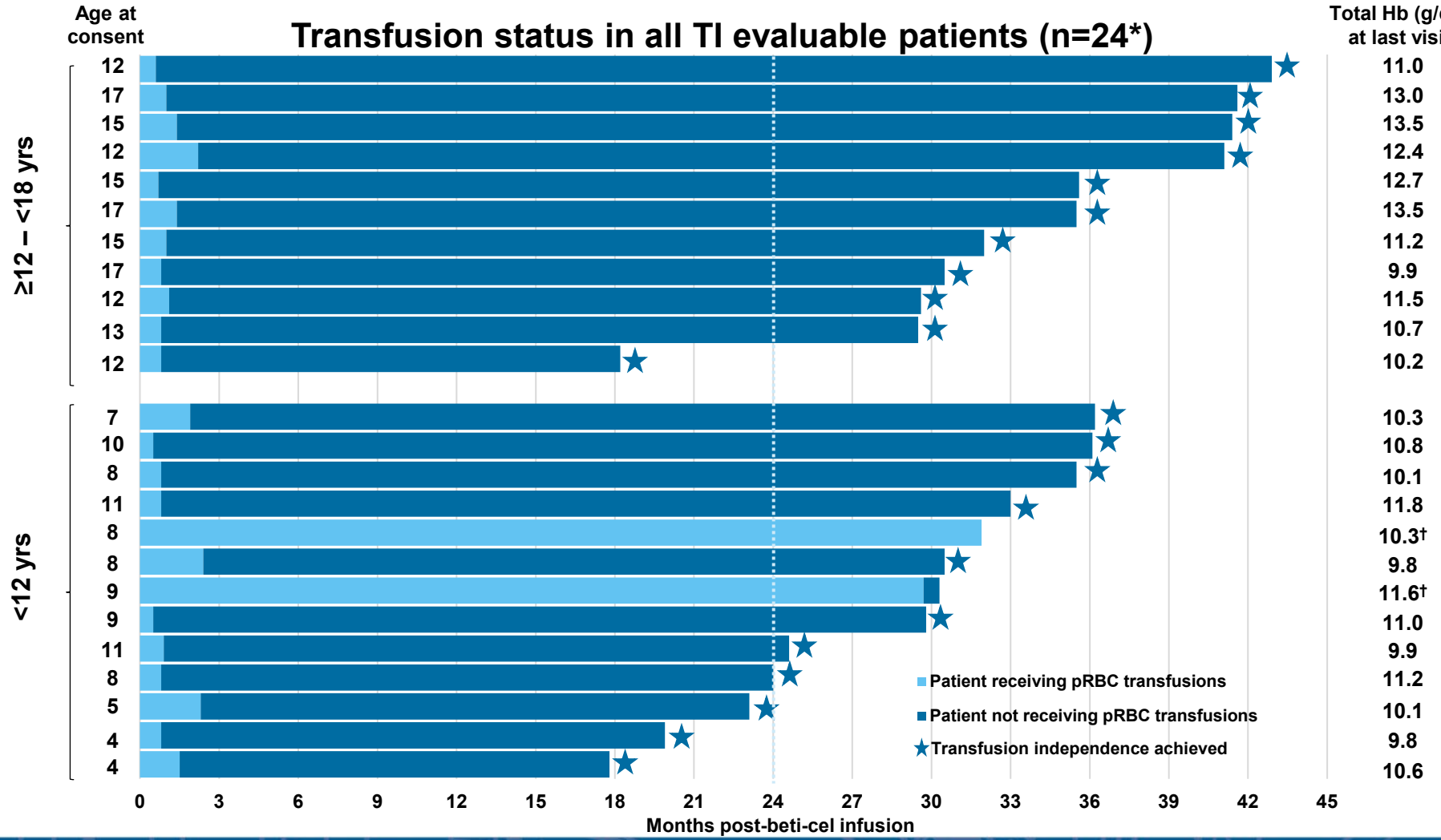
Drug product and conditioning characteristics

	<12 yrs N=16	≥12 – <18 yrs N=11	≥18 yrs N=14
Drug product characteristics			
Vector copy number, vector copies/diploid genome	**2.9** (1.9 – 7.0)	**3.3** (1.2 – 6.0)	**3.0** (1.9 – 5.6)
CD34+ cells transduced, %	**72** (34 – 94)	**82** (34 – 90)	**78** (53 – 90)
Cell dose, CD34+ cells x 10^6/kg	**10.2** (6.1 – 42.1)	**7.4** (5.0 – 19.4)	**8.9** (5.2 – 13.6)
Conditioning			
Estimated daily average AUC over 4 days, µM*min	**4145** (3605 – 7497)	**4471** (3708 – 8947)	**4517** (3824 – 9086)
Busulfan dosing q6h, n (%)	**8** (50)	**8** (73)	**4** (29)
Busulfan dosing q24h, n (%)	**8** (50)	**3** (27)	**10** (71)
Engraftment			
ANC ≥500 cells/µL x 3 days	**26** (17 – 39)	**26** (16 – 38)	**21** (13 – 27)
Platelets ≥20,000 cells/µL x 3 days	**51** (20 – 94)	**50** (25 – 84)	**43** (21 – 58)

Values are median (min – max) unless stated otherwise.
ANC, absolute neutrophil count; AUC, area under the curve.

Data cut-off: August 18, 2021

22/24 (92%) evaluable pediatric patients maintained TI



11/11 patients ≥12 – <18 yrs achieved TI

- **Median duration of ongoing TI: 31.2** (15.1 – 40.1) months
- **Median weighted average Hb during TI: 11.6** (9.8 – 13.4) g/dL

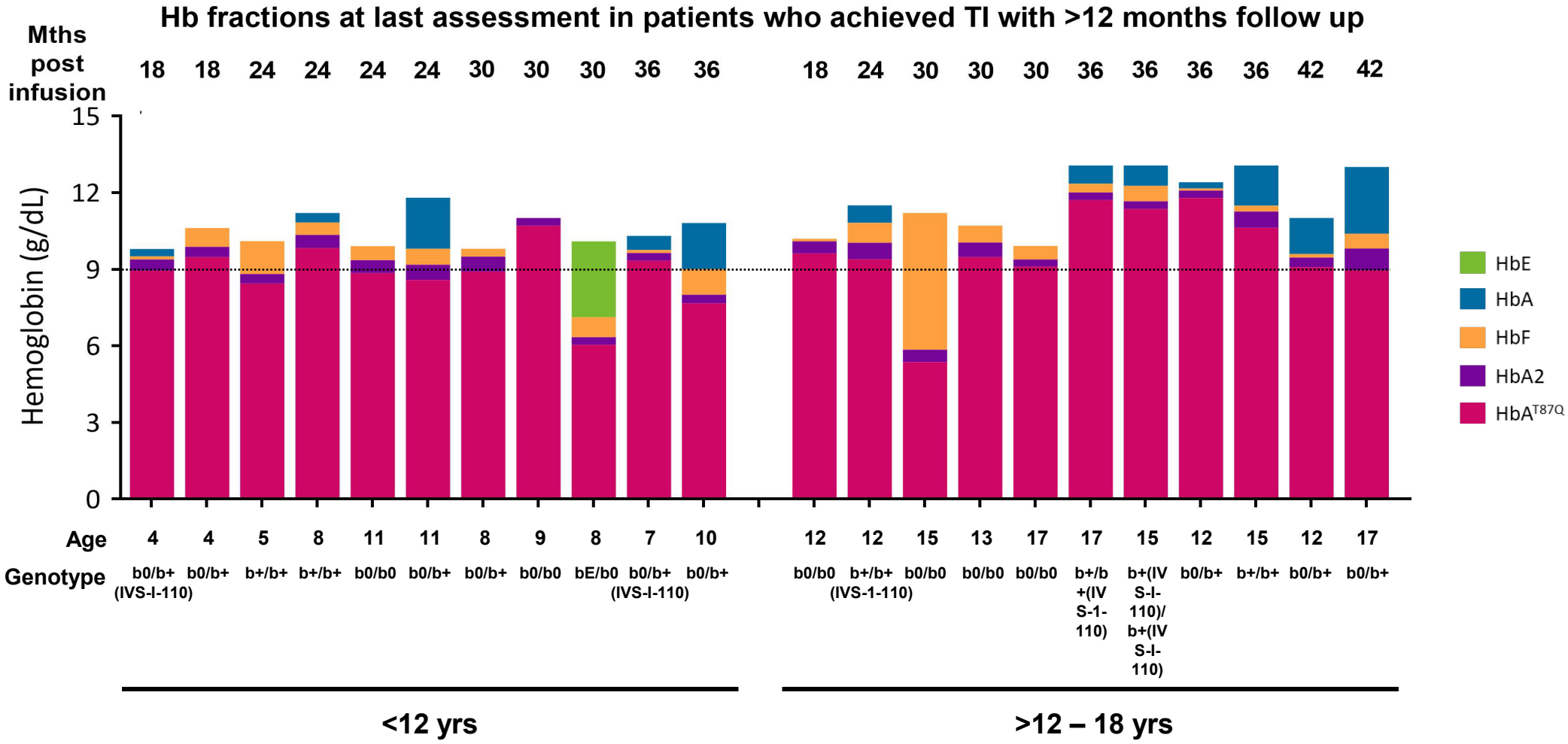
11/13 patients <12 yrs achieved TI

- **Median duration of ongoing TI: 25.5** (13.3 – 32.7) months
- **Median weighted average Hb during TI: 10.0** (9.7 – 11.5) g/dL

*Three patients were not TI evaluable at the time of analysis. †Hb supported by packed RBC transfusions.
Values are median (min – max) unless stated otherwise. Blue dotted line denotes completion of parent study and enrollment in LTF-303.
Hb, hemoglobin; RBC, red blood cell; TI, transfusion independence (defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥ 12 months); yrs, years.

Data cut-off: August 18, 2021

Gene therapy–derived HbA^{T87Q} has driven total Hb expression in patients who achieved TI

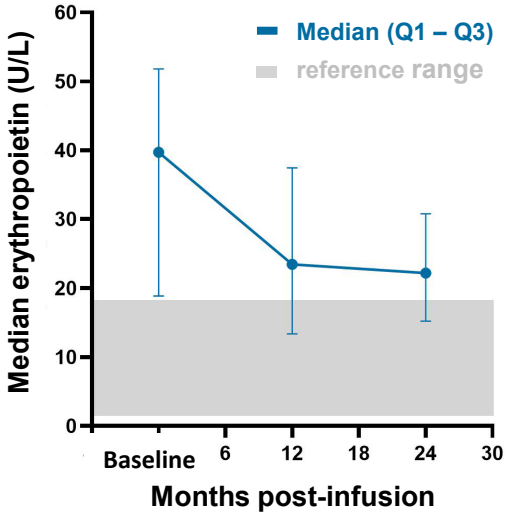


Hb reference range: <12 yrs female/male: 11.5 – 16.0 g/dL; ≥12 – <18 yrs female: 12.0 – 15.0 g/dL; ≥12 – < 18 yrs male: 12.5 – 16.1 g/dL per American College of Clinical Pharmacy. Reference values for common laboratory tests Pediatric Self-Assessment Program. Black dotted line denotes TI.
Hb, hemoglobin; HbA^{T87Q}, Hb with modified β-globin gene ($\beta^{A\text{-}T87Q}$); TI, transfusion independence (defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months); yrs, years.

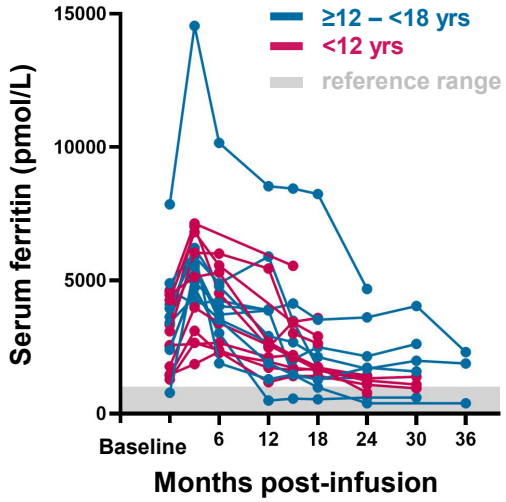
Data cut-off: August 18, 2021

Biomarkers of ineffective erythropoiesis trended towards normal levels in patients achieving TI

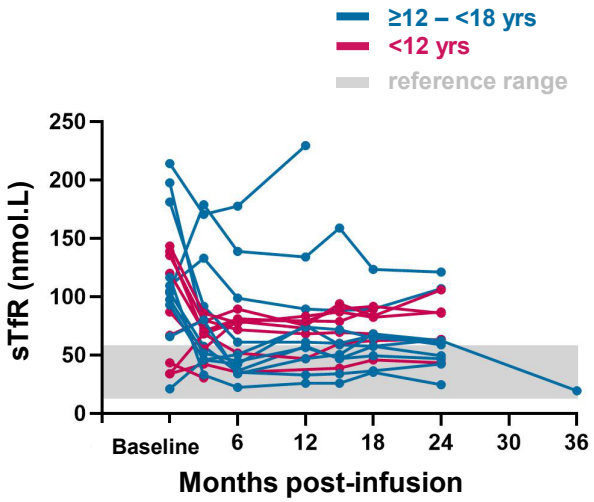
A. Erythropoietin



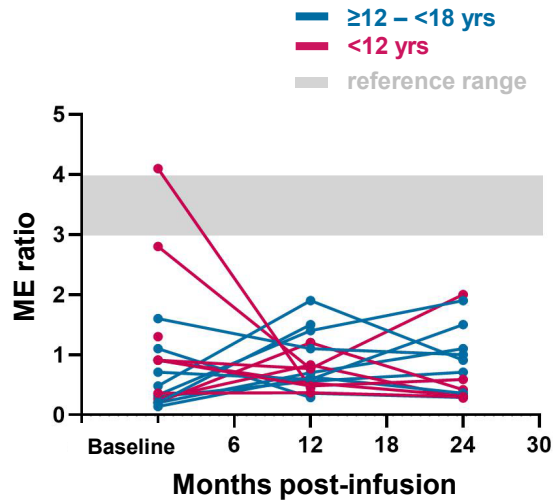
B. Serum Ferritin



C. Soluble Transferrin Receptor



D. Myeloid:Erythroid ratio



45% (9/20) of patients had increased M:E ratio at Month 12 vs baseline

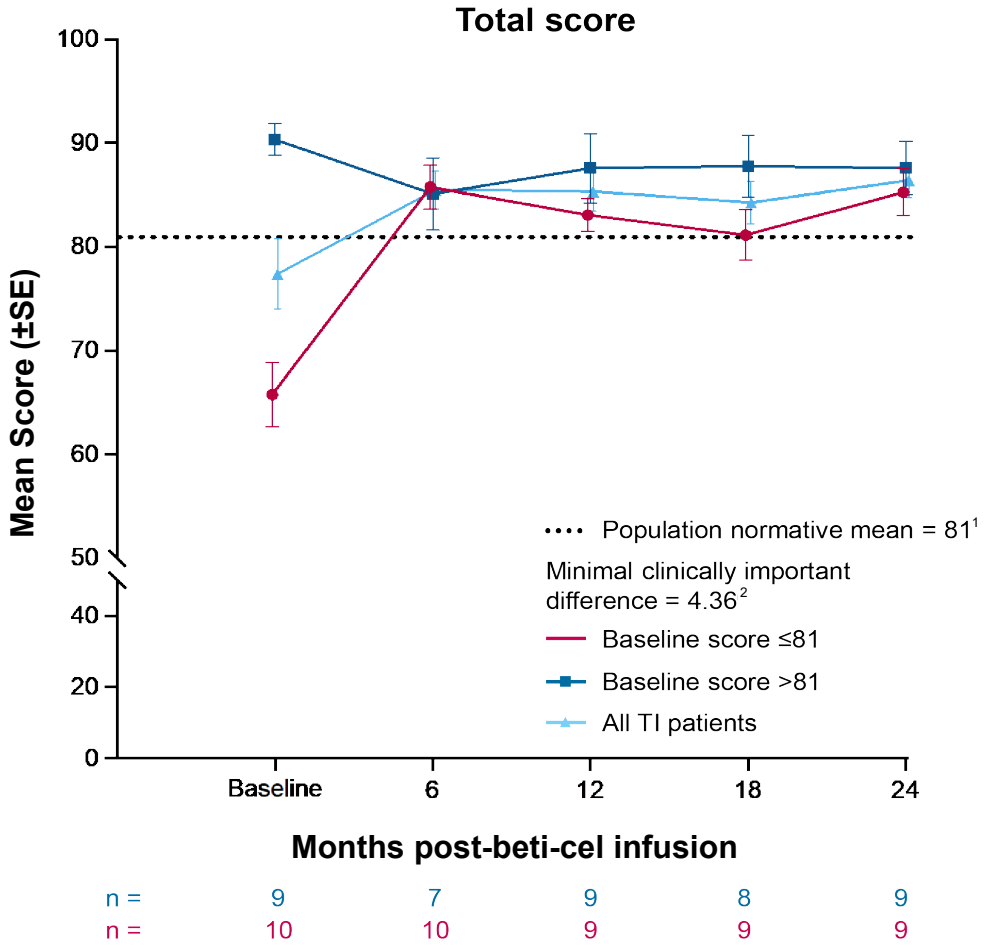
Data presented here are from an earlier interim data-cut (March 2021).

Kulozik, A. (2021, June 9–17). *Interim results of betibeglogene autotemcel gene therapy in paediatric patients with transfusion-dependent β-thalassemia (TDT) treated in the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies* [Poster Presentation EP1301]. European Hematology Association, Virtual.

ME, myeloid:erythroid ratio; sTfR, soluble transferrin receptor; TI, transfusion independence (defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months).

Patient-reported QoL scores improved from baseline

- Of pediatric/adolescent patients who achieved TI, the mean PedsQL total score increased compared with baseline and improvements were ~2-fold the MCID
  - Increases were greater in patients with baseline scores ≤pop norm; similar trends in physical and psychosocial domains



1. Ow N, et al. *Qual Life Res.* 2020;29(9):2311-2332; 2. Varni JW, et al. *Ambul Pediatr.* 2003;3(6):329-341.
MCID, minimal clinically important difference; PedsQL, Paediatric Quality of Life measurement for Paediatric Quality of Life Inventory; QoL, quality of life; TI, transfusion independence (defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months.

Safety profile

- Four AEs related/possible related to beti-cel
  - Day of infusion: tachycardia (n=1, Grade 1) and abdominal pain (n=2, Grade 1)
  - Post-infusion: non-serious thrombocytopenia (n=1, Grade 3), non-serious dysplasia (n=1, Grade 1)
- Veno-occlusive liver disease treated by defibrotide in 3 patients and resolved
  - 2 were serious, Grade 4 events in patients 12 years of age
- No vector-derived replication-competent lentivirus, or events of insertional oncogenesis or hematologic malignancy reported
- All patients were alive at last follow-up

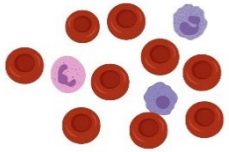
Non-hematologic grade ≥ 3 AEs* *Post beti-cel infusion in ≥4 patients*	**N = 27 n (%)**
Stomatitis	15 (56)
Epistaxis	6 (22)
Decreased appetite	5 (19)
Pyrexia	4 (15)
Serious AEs *Post beti-cel infusion in ≥2 patients*	
Pyrexia	5 (19)
Febrile neutropenia	2 (7)
Neutropenia	2 (7)
Stomatitis	2 (7)
Thrombocytopenia	2 (7)
Veno-occlusive liver disease†	2 (7)

*Hematologic AEs commonly observed post-transplantation were excluded.
†One additional patient had a non-serious veno-occlusive liver disease event.

AE, adverse event.

Conclusions: Outcomes in pediatric patients treated with beti-cel

- Pediatric patients across TDT genotypes achieved TI rates (92% [22/24]) over a median follow-up of 30.4 months which was comparable to adults (85.7% [12/14])



- TI was maintained by stable expression of GT-derived adult Hb (HbA^{T87Q})
  - Previous interim data report improvements in ineffective erythropoiesis in patients achieving TI[1]
- Weighted average Hb during TI was within normal or near-normal ranges

- Patient-reported QoL scores showed clinically-meaningful improvements from baseline

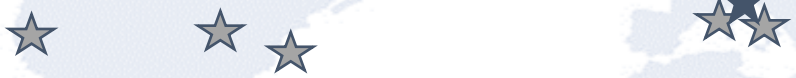
- Safety profile was dominated by the know effects of single-agent busulfan myeloablation
- No vector-derived replication-competent lentivirus, events of insertional oncogenesis or hematologic malignancy reported

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

1. Kulozik et al. EHA 2021 Abstract EP1301.

GT, gene therapy; Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence (defined as weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months); QoL, quality of life.

Thank you to the study participants and their families



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