EHA 2020 Virtual Congress Abstract: S296

Improvement in erythropoiesis in patients with transfusion-dependent β-thalassemia following treatment with betibeglogene autotemcel (LentiGlobin for β-thalassemia) in the Phase 3 HGB-207 study

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Disclosure

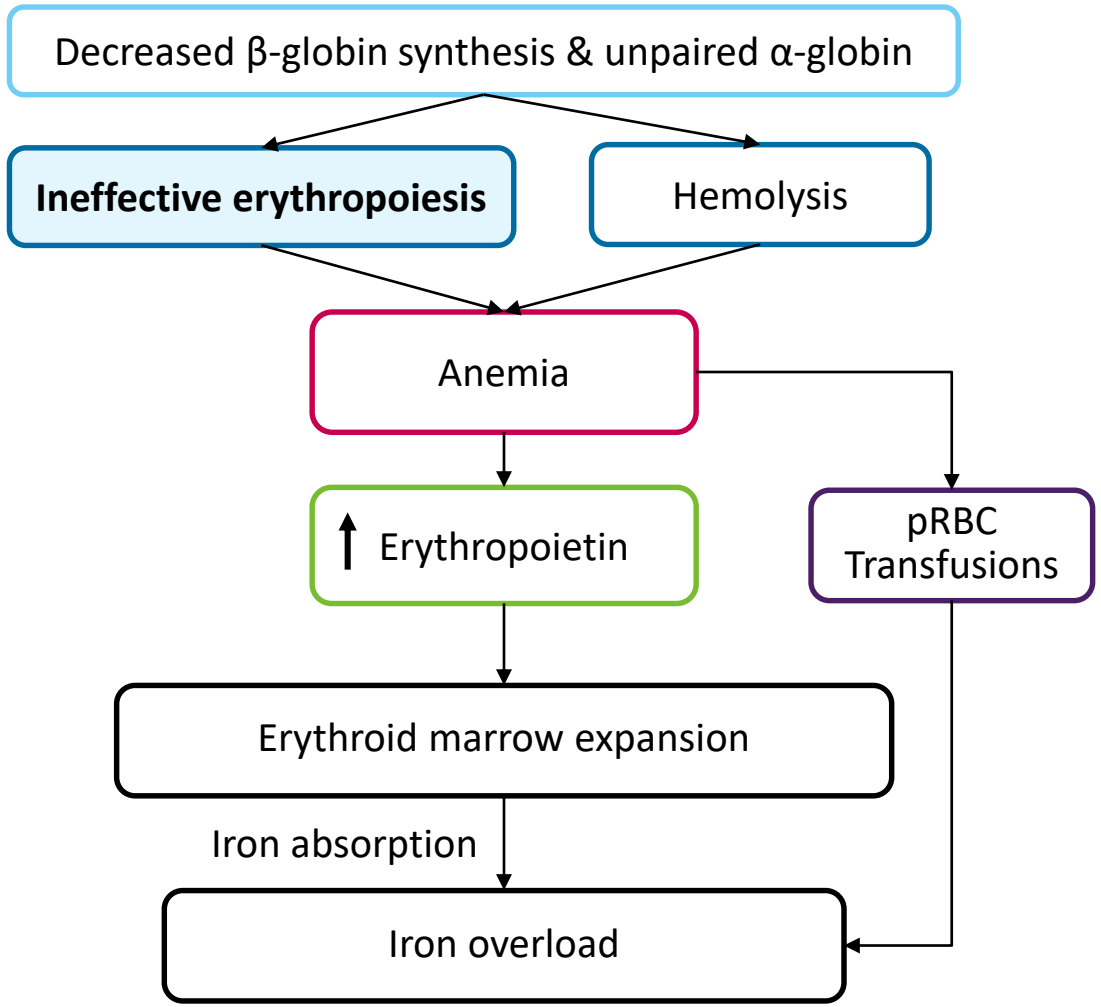
John Porter

- Consultancy, honoraria: bluebird bio, Agios, Celgene, Protagonism, Vifor, Silence Therapeutics, La Jolla Therapeutics

Live Q&A Panel Discussion: Wednesday, June 17, 2020, 19:00 – 19:45 (CEST)

Program section: New therapeutic approaches for thalassemia

Ineffective erythropoiesis is a hallmark of β-thalassemia



- Impaired β-globin production leads to ineffective erythropoiesis characterized by suboptimal erythrocyte production[1-3]
  - Erythropoietin levels are increased, stimulating the proliferation and differentiation of erythroid progenitors[1-3]
  - Maturation of erythroblasts into erythrocytes is impaired[1-3]
- Patients with transfusion-dependent β-thalassemia (TDT) present with severe anemia and require lifelong pRBC transfusions resulting in iron overload[1-3]
  - Hepcidin levels are decreased and serum ferritin levels are increased[3]
  - Iron overload results in organ damage, which is the main driver of mortality[1-3]

1. Oliveri NF. N Engl J Med 1999; 341:99-109. 2. Oikonomidou and Rivella. *Blood Rev.* 2018;32(2): 130–143. 3. Ribeil JA, et al. *Scientific World Journal*. 2013 Mar 28;2013:394295.

pRBC, packed red blood cell

Northstar-2 (HGB-207) Phase 3 study of betibeglogene autotemcel

(beti-cel; LentiGlobin for β-thalassemia)

Background

- In the phase 1/2 studies, 11/14 patients with non-β^0/β^0 genotypes achieved transfusion independence with up to 5 years of follow-up[1,2]
- HGB-207 is evaluating outcomes using a refined drug product manufacturing process

HGB-207

Key eligibility criteria

- Transfusion-dependent β-thalassemia
- Non-β^0/β^0 genotype
- ≤ 50 years of age

Primary endpoint: **Transfusion Independence**

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

Key secondary and exploratory endpoints:

- TI characteristics
- Assessment of ineffective erythropoiesis

Study disposition

Consented
N=31

Ineligible
N=8*

Stem cell mobilization complete
N=24

Discontinued
N=1†

beti-cel infused
N=23 (Enrollment complete)

Completed HGB-207 and enrolled in LTF-303
N=9

Median follow-up:
19.4 months
(min – max: 1.2 – 36.2 months)

*Screen failures due to advanced liver disease (n=5) and withdrew consent (n=3)
†1 patient withdrew after mobilization due to pregnancy

1. Kwiatkowski et al. ASH 2019. Abstract 4628. 2. Magrin et al. ASH 2019. Abstract 3358.

Hb, hemoglobin; pRBC, packed red blood cell; TDT, transfusion-dependent β-thalassemia

Interim datacut: Last patient visit: 3 March 2020; Database lock: 7 April 2020

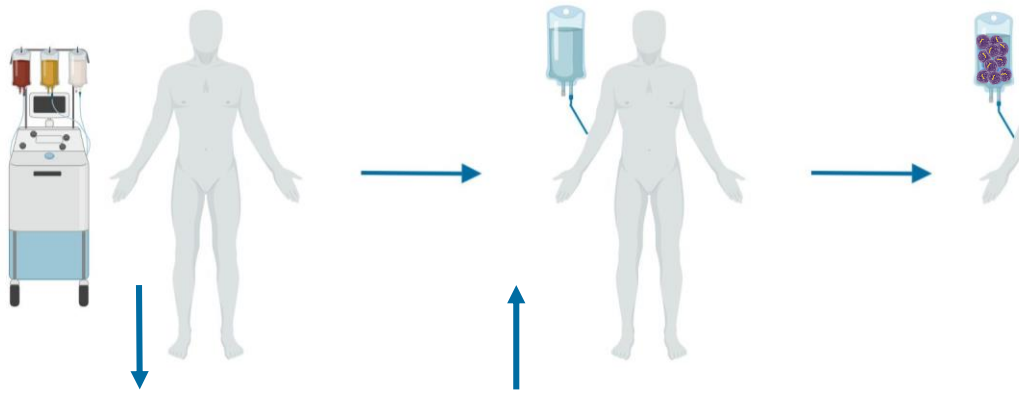
HGB-207: Study design

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

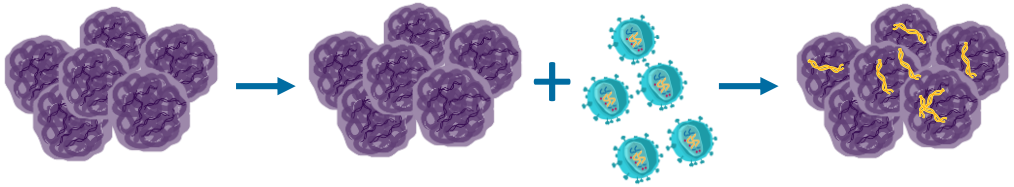
Busulfan myeloablative conditioning

beti-cel IV infusion

Transduced HSCs engraft and reconstitute RBCs which contain HbA^{T87Q}



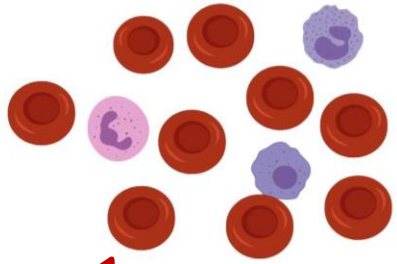
Drug product centralized manufacturing



Select CD34+ cells

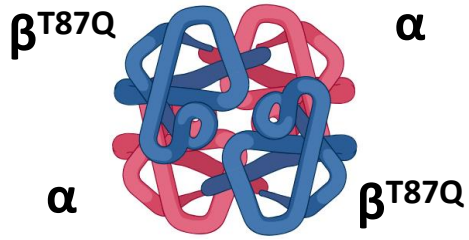
HSCs transduced with BB305 lentiviral vector (encodes for β$^{A\text{-}T87Q}$-globin)

Cryopreserve, test, release drug product



HbA^{T87Q}

- Gene-therapy derived functional Hb
- Measurable by HPLC



2-year follow-up

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

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

HGB-207: Patient characteristics

Parameters		N = 23
Genotypes n, (%)	β^+/β^0	**12** (52)[†]
	β^E/β^0	**6** (26)
	β^+/β^+	**5** (22)[‡]
Age at consent, median (min – max), yrs		**15** (4 – 34)
< 12 years, n (%)		**8** (35)
≥ 12 – < 18 years, n (%)		**6** (26)
≥ 18 years, n (%)		**9** (39)
Liver iron concentration median (min – max), mg Fe/g dw		**5.3** (1 – 41)
Cardiac T2* median (min – max), msec		**36.7** (21 – 57)
Splenectomy, n (%)		**4** (17)

[†] Includes 2 patients who are heterozygous for the β⁺IVS1-5 mutation
[‡] Includes 2 patients who are heterozygous for the β⁺IVS1-110 mutation and 2 patients homozygous for the β⁺IVS1-5 mutation

Pre-study pRBC transfusion history Retrospective data 2 years prior to enrollment	**N = 23** median (min – max)
Volume, mL/kg/yr	**207.9** (142.1 – 274.4)
Number, transfusion episodes/yr	**16.0** (11.5 – 37.0)
Pre-transfusion Hb, g/dL	**9.6** (7.5 – 11.0)

Hb, hemoglobin; pRBC, packed red blood cells

HGB-207: Mobilization, drug product, conditioning, and engraftment characteristics

	N = 23
Mobilization cycles/patient, n (%)	
1	**18** (78)
2	**5** (22)
Drug product characteristics (average/patient)	median (min – max)
Vector copy number, vector copies/diploid genome	**3.3** (1.9 – 5.6)
CD34+ cells transduced, %	**78** (34 – 90)
Cell dose, CD34+ cells x 10^6/kg	**8.7** (5.0 – 19.9)
Conditioning characteristics Target busulfan AUC: q24h: 4200 (min – max: 3800 – 4500) µM*min; q6h: 1050 (min – max: 950 – 1125) µM*min	
Estimated daily average AUC over 4 days, µM*min	**4337** (3708 – 8947)
Engraftment characteristics	
Neutrophil engraftment, ANC ≥ 500 cells/µL x 3 days, days	**23** (13 – 32)
Platelet engraftment, ≥ 20,000 platelets/µL x 3 days, days	**46** (20 – 94)

Median duration of hospitalization: 45 (min – max: 30 – 92) days

ANC, absolute neutrophil counts; AUC, area under the curve

HGB-207: Safety summary post-beti-cel infusion

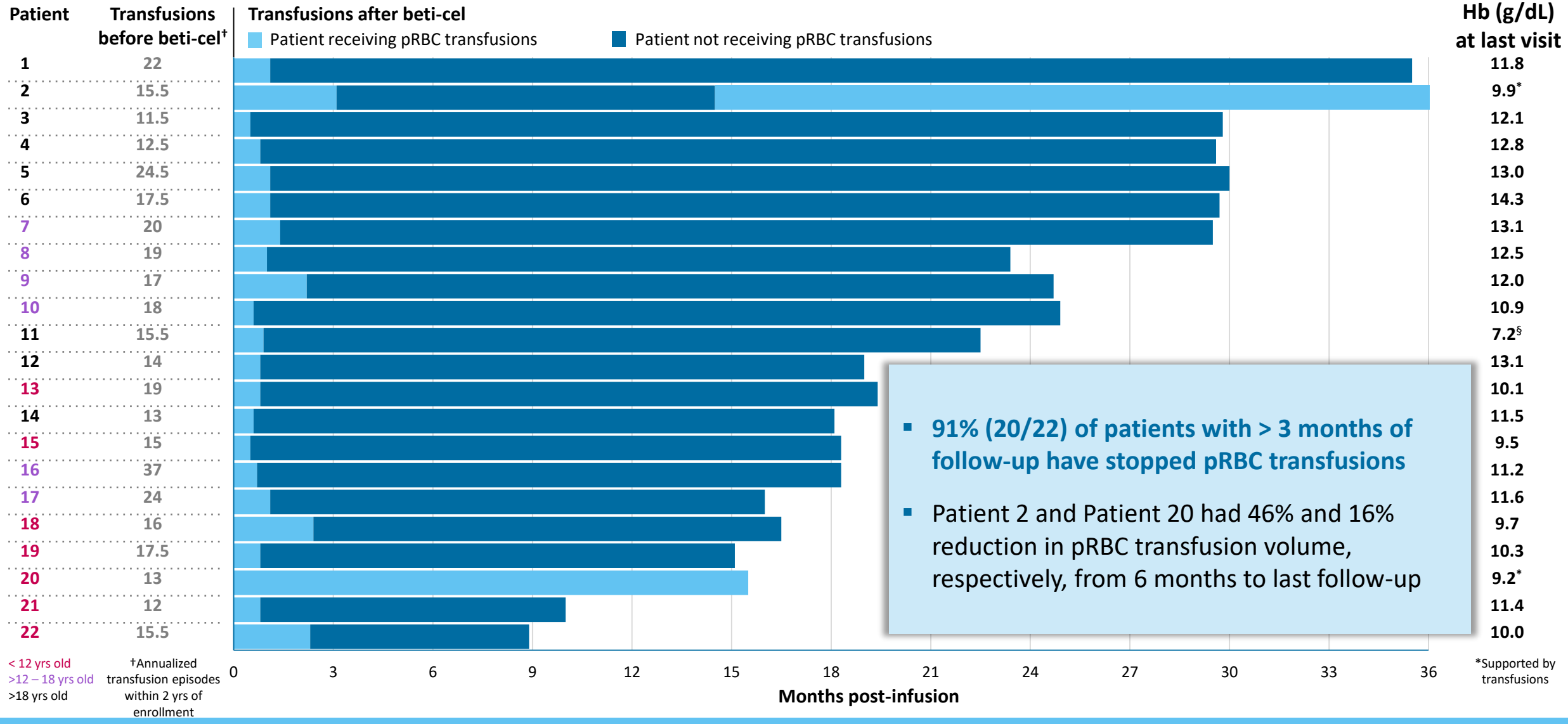
Non-hematologic grade ≥ 3 AEs* *Post beti-cel infusion in ≥ 3 patients*	**N = 23 n (%)**
Stomatitis	14 (61)
Febrile neutropenia	8 (35)
Epistaxis	5 (22)
Pyrexia	4 (17)
Decreased appetite	3 (13)
Veno-occlusive liver disease	3 (13)
Serious AEs *Post beti-cel infusion in ≥ 2 patients*	
Veno-occlusive liver disease	3 (13)
Thrombocytopenia	2 (9)

*Hematologic AEs commonly observed post-transplantation have been excluded

- AEs considered related or possibly related to the drug product:
  - Day of infusion:
    - Tachycardia (n = 1, Grade 1)
    - Abdominal pain (n = 1, Grade 1)
  - Post-infusion:
    - One serious Grade 3 event of thrombocytopenia (Day +114 to +163)
    - One nonserious Grade 3 event of thrombocytopenia (Day +93 – ongoing)
    - Pain in extremity (n = 1, Grade 1)
- 3/23 patients experienced serious VODs (all Grade 4)
  - 1/3 patients who had a serious VOD event received prophylaxis (ursodiol)
  - 17/20 patients who did not have a VOD received VOD prophylaxis
    - 12, ursodiol alone; 4, ursodiol + defibrotide; 1, defibrotide alone
  - All serious VOD events resolved following treatment with defibrotide
- No graft failure
- All patients remain alive
- No complications related to the lentiviral vector including replication-competent lentivirus or clonal dominance

AE, adverse event; VOD, veno-occlusive liver disease

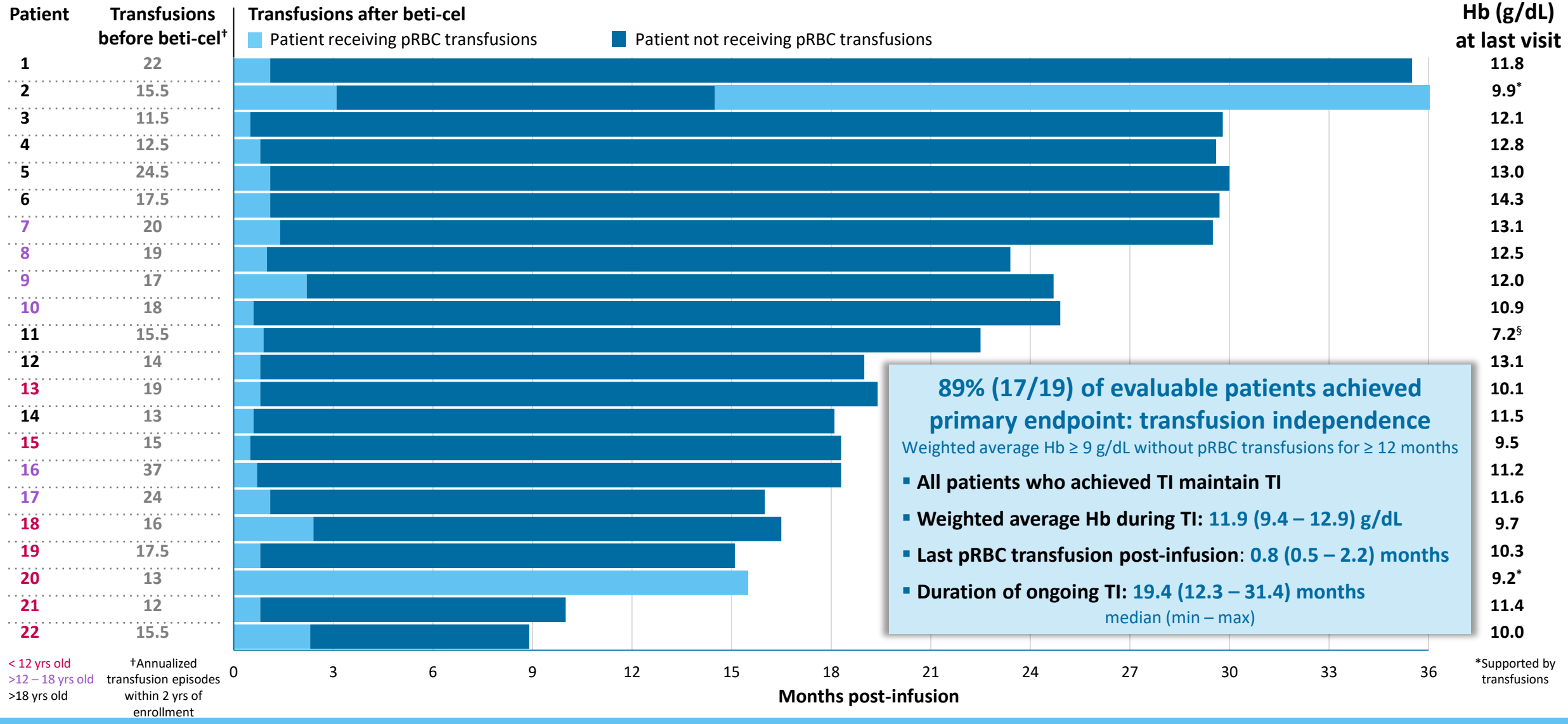
HGB-207: Transfusion status post-beti-cel infusion in patients with > 3 months follow-up



- **91% (20/22) of patients with > 3 months of follow-up have stopped pRBC transfusions**
- Patient 2 and Patient 20 had 46% and 16% reduction in pRBC transfusion volume, respectively, from 6 months to last follow-up

§Patient's total Hb level at Month 22 was 13.4 g/dL. Following a planned orthopedic surgery, the patient had blood loss, which required 1 pRBC transfusion; Hb, hemoglobin; pRBC, packed red blood cell

HGB-207: Transfusion status post-beti-cel infusion in patients with > 3 months follow-up

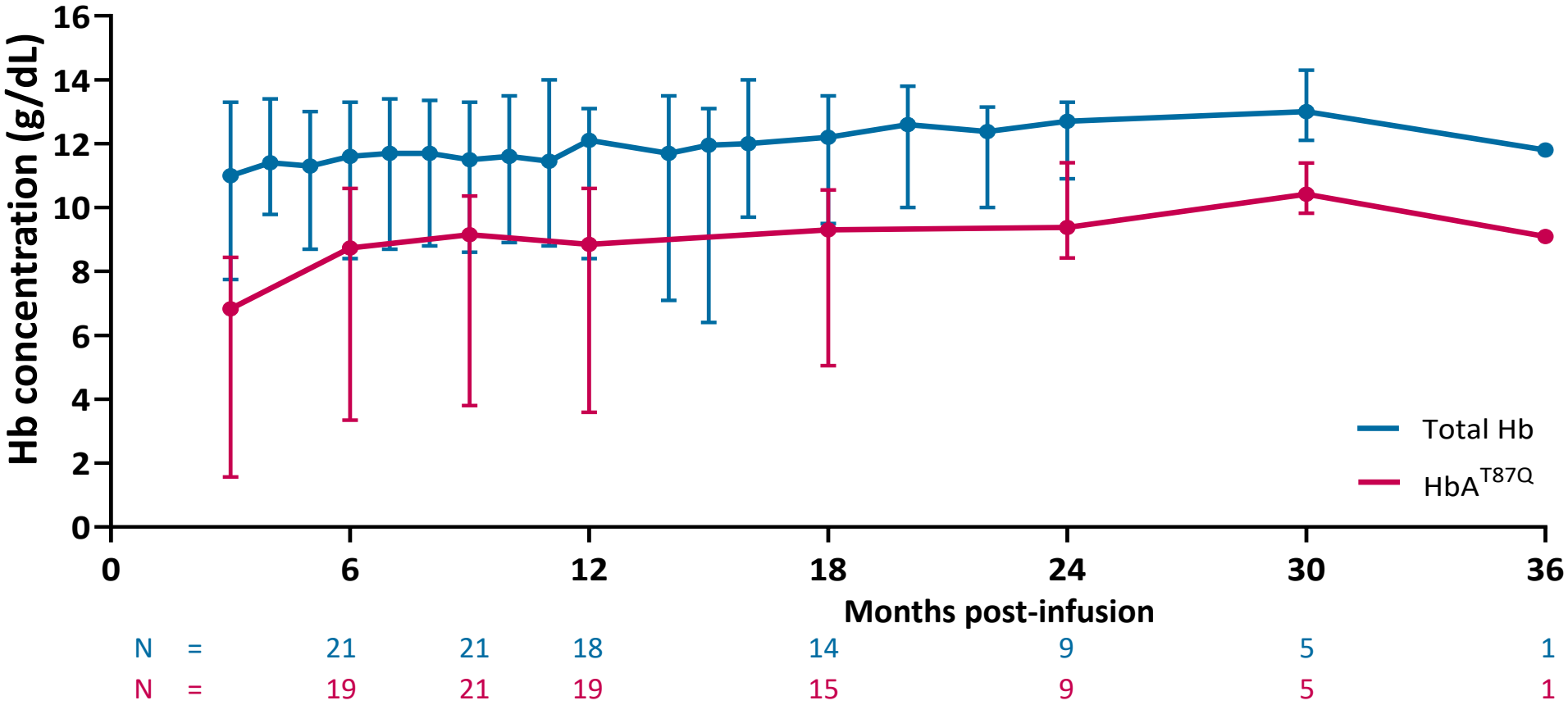


§Patient's total Hb level at Month 22 was 13.4 g/dL. Following a planned orthopedic surgery, the patient had blood loss, which required 1 pRBC transfusion; Hb, hemoglobin; pRBC, packed red blood cell

HGB-207: Median unsupported total Hb is ≥ 11.5 g/dL after beti-cel gene therapy

Hemoglobin in patients who have not received a transfusion in ≥ 60 days

	M6	M9	M12	M18	M24	M30	M36
Total Hb (g/dL)	11.6	11.5	12.1	12.2	12.7	13.0	11.8
HbA^{T87Q} (g/dL)	8.7	9.1	8.9	9.3	9.4	10.4	9.1



N =	21	21	18	14	9	5	1
N =	19	21	19	15	9	5	1

HbA^{T87Q} contributed >70% to the total Hb at M12 in patients who achieved TI

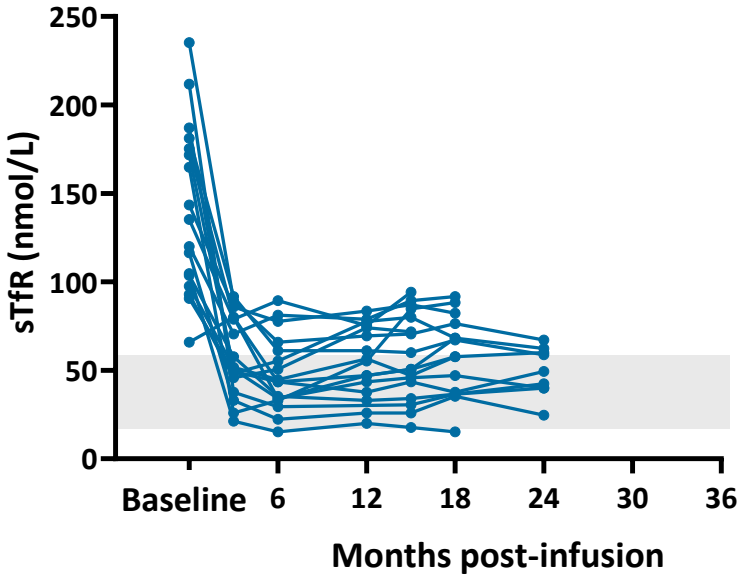
In patients who did not achieve TI:

- At M12, total Hb and HbA^{T87Q} in Patient 2 was 8.4 g/dL and 3.6 g/dL, respectively; HbA^{T87Q} decreased to 0.9 g/dL at M24
- At M12, total Hb and HbA^{T87Q} in Patient 20 was 13.4 g/dL and 0.9 g/dL, respectively

Median (min – max) depicted; Hb, hemoglobin; TI, transfusion independence

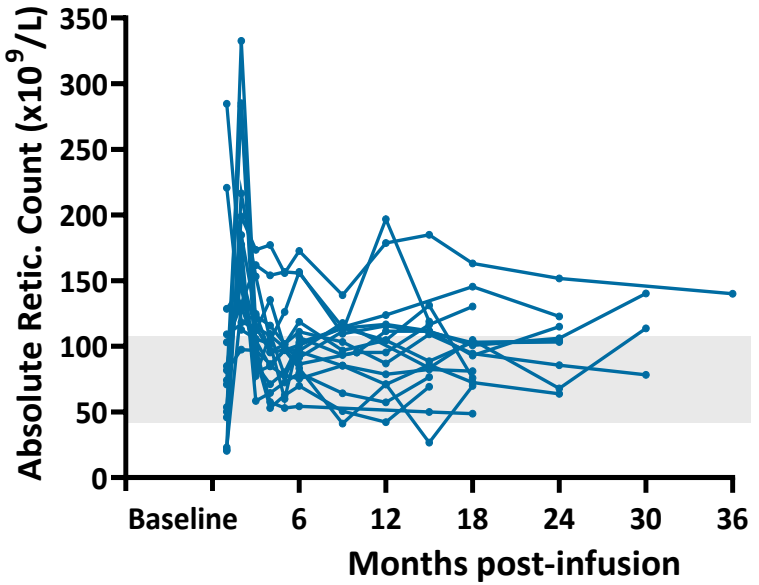
HGB-207: Biomarkers of ineffective erythropoiesis improved in patients who achieved transfusion independence

Soluble transferrin receptor (sTfR)



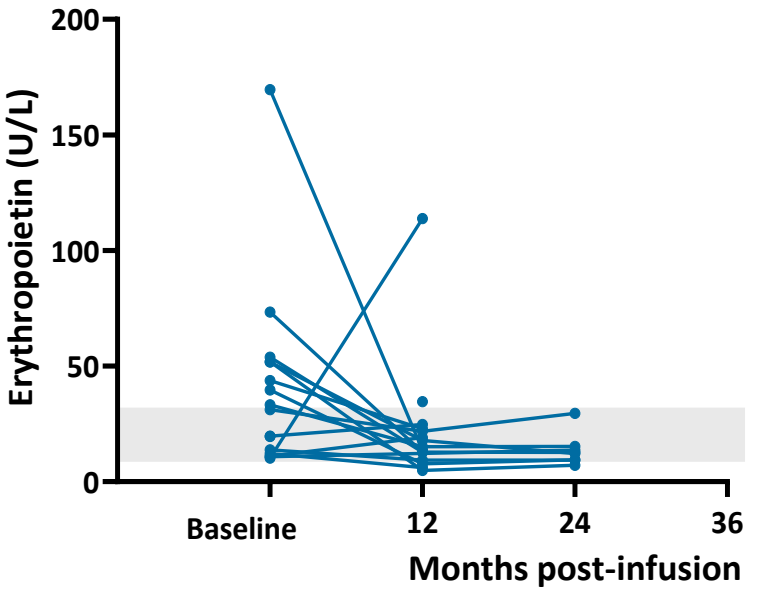
N = 17 17 16 15 9 0 0

Absolute reticulocyte count



N = 16 17 15 14 9 3 1

Erythropoietin



N = 16 15 8 0

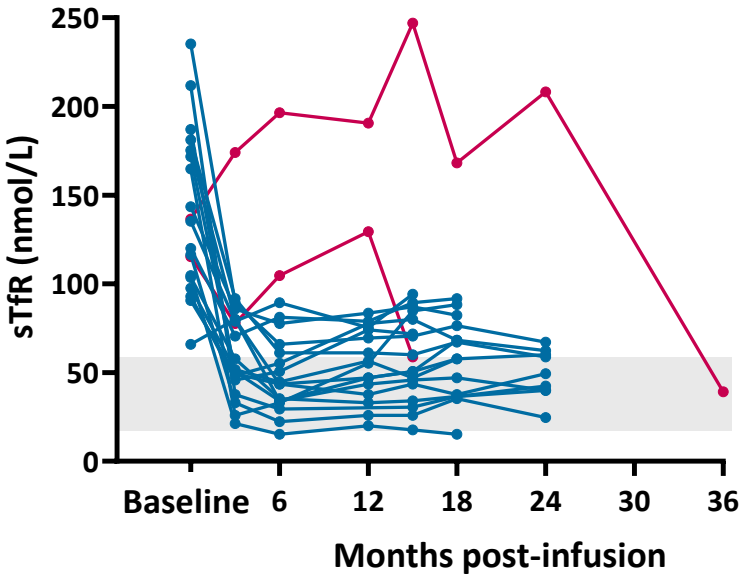
sTfR, reticulocytes, and erythropoietin trend toward normal in patients who achieved transfusion independence

Blue lines indicate patient who achieved TI

Gray bar indicates reference range; TI, transfusion independence

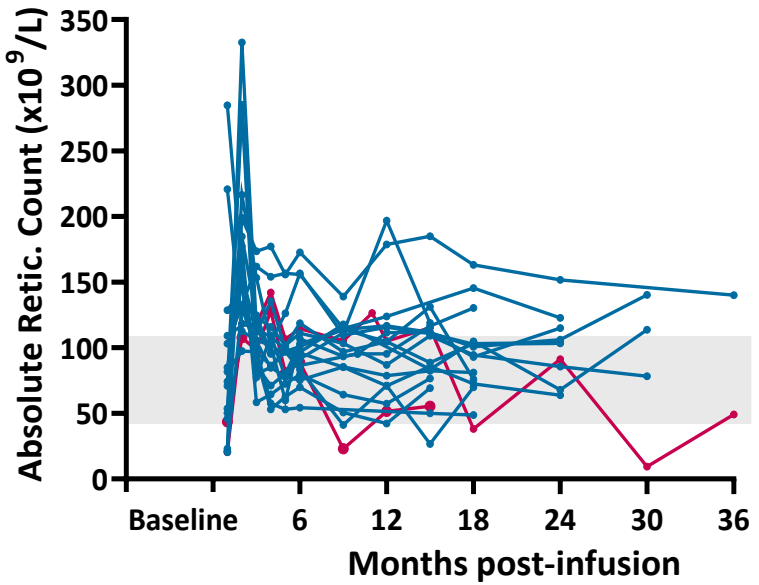
HGB-207: Biomarkers of ineffective erythropoiesis improved in patients who achieved transfusion independence

Soluble transferrin receptor (sTfR)



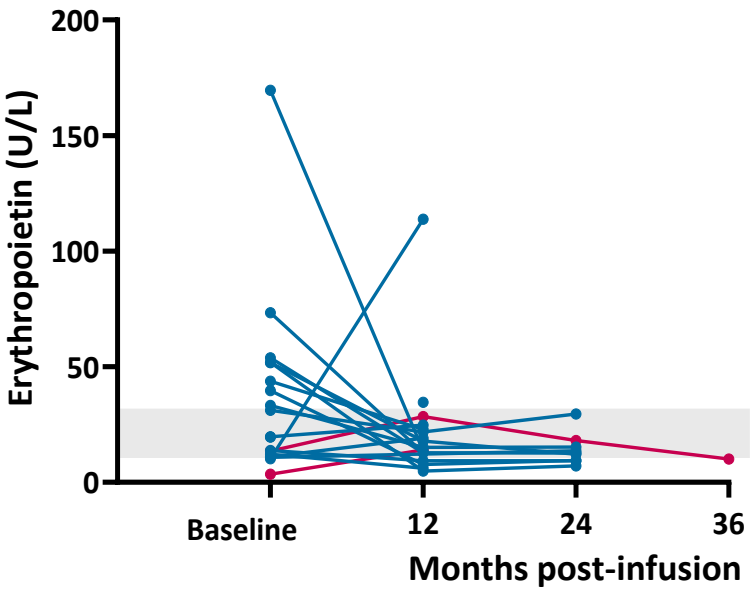
N =	19	19	18	16	10	0	1

Absolute reticulocyte count



N =	18	19	17	15	10	4	2

Erythropoietin



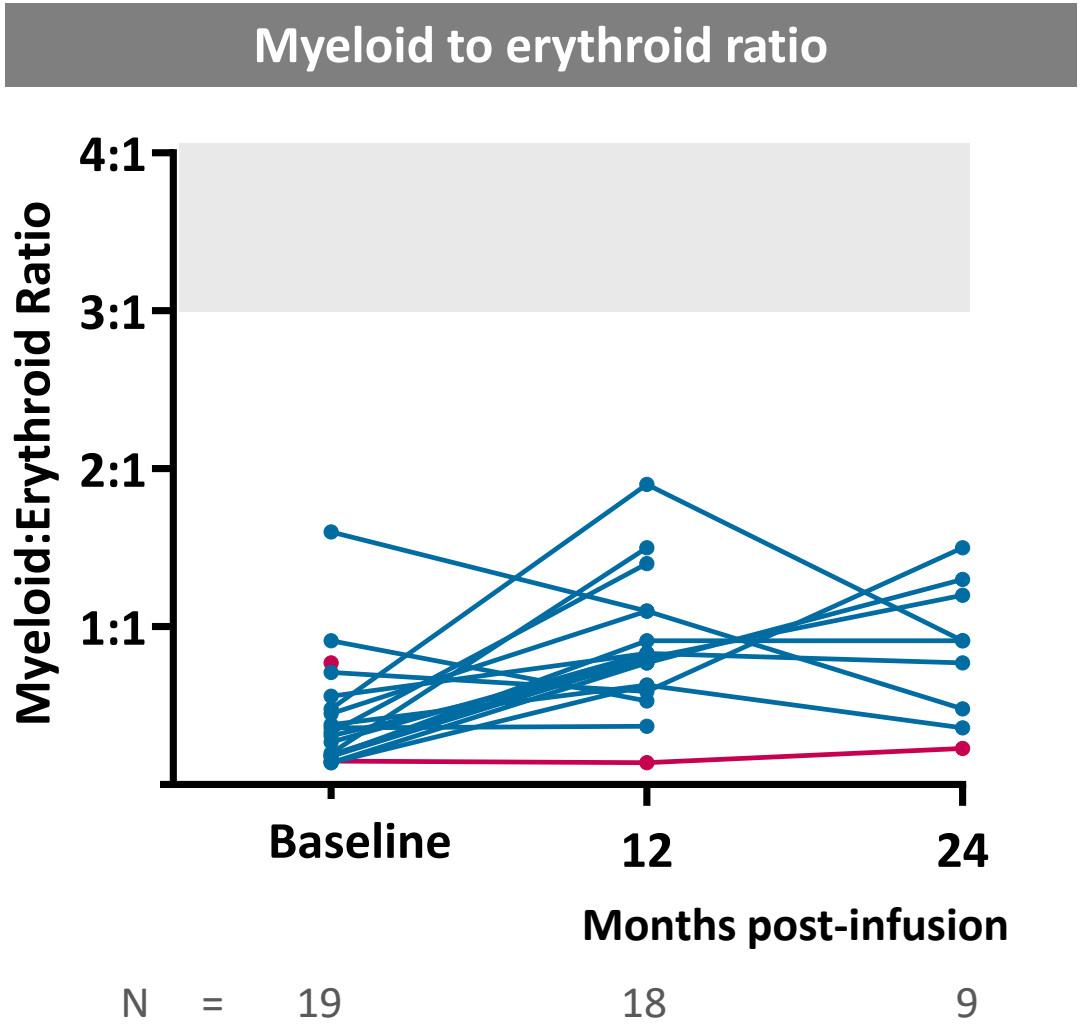
N =	18	17	9	1

sTfR, reticulocytes, and erythropoietin trend toward normal in patients who achieved transfusion independence

Blue lines indicate patient who achieved TI
Red lines indicate patients who were evaluable, but did not achieve TI

Gray bar indicates reference range; TI, transfusion independence

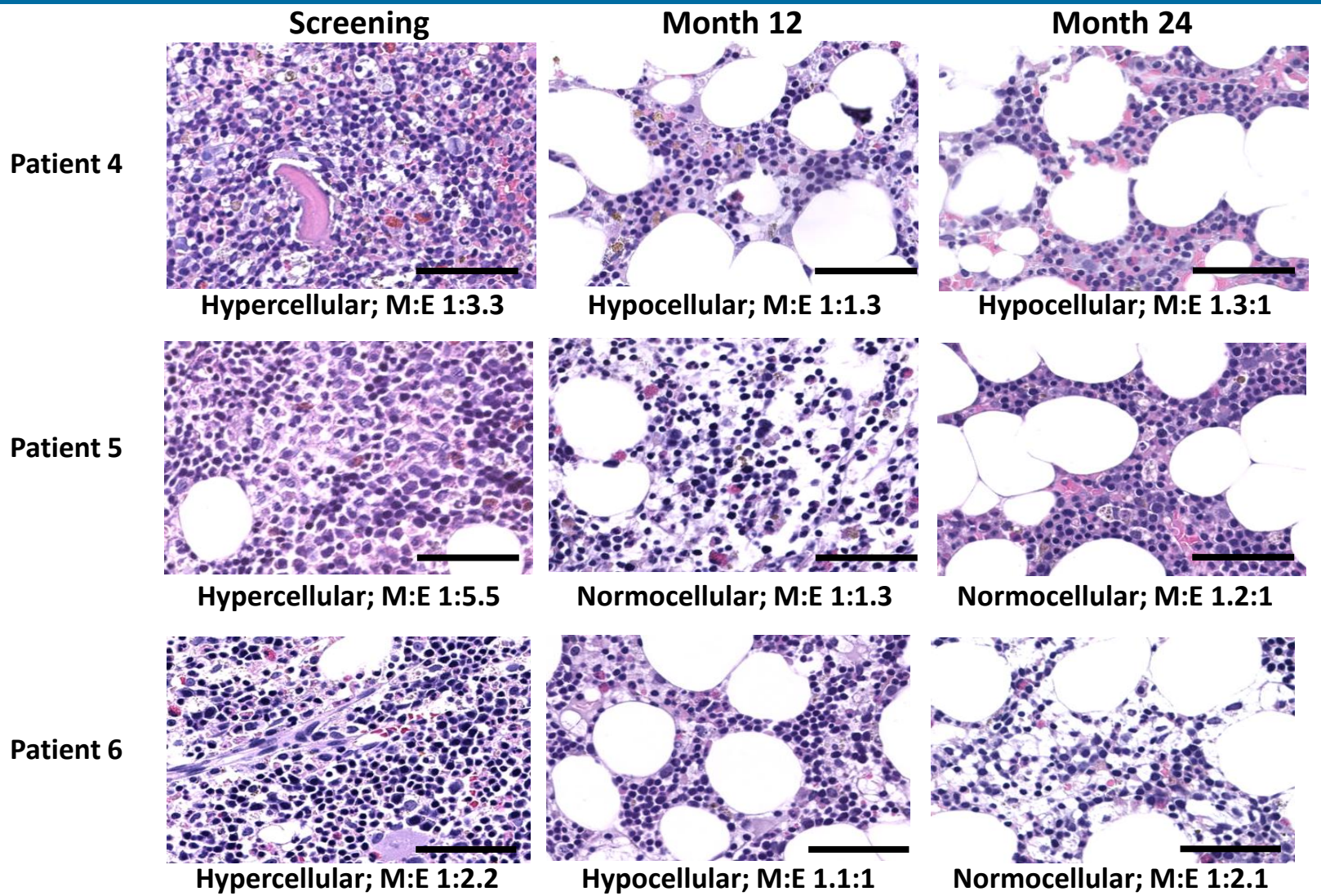
HGB-207: Myeloid:erythroid ratios improved in patients who achieved transfusion independence



Blue lines indicate patient who achieved TI
Red lines indicate patients who were evaluable, but did not achieve TI

Gray bar indicates reference range[1]; TI, transfusion independence; 1. Origa R. GeneReviews®. 2018.

HGB-207: Bone marrow cellularity in patients who achieved transfusion independence



Bone marrow histology after beti-cel gene therapy improved compared to screening

- 5/14* patients who achieved TI had normocellular bone marrow at Month 12
- 4/8* patients who achieved TI had normocellular bone marrow at Month 24

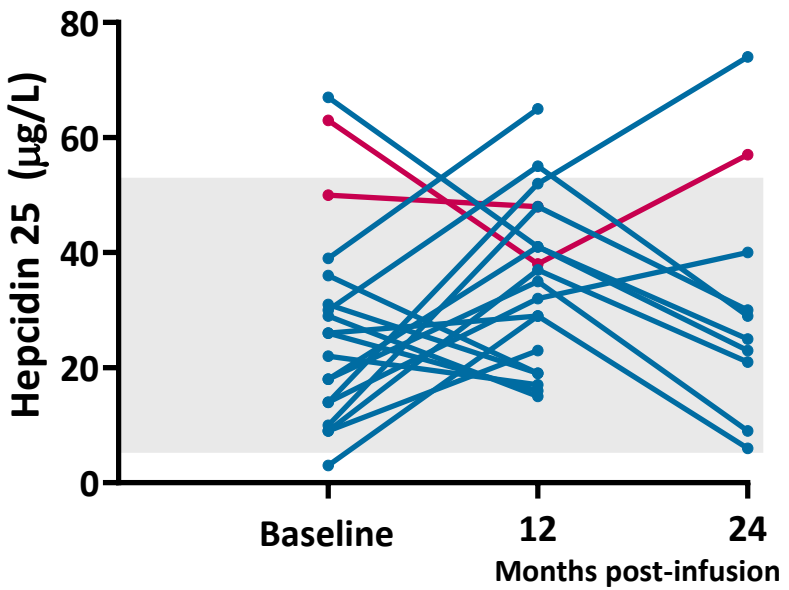
Scale bars: 50 µm. *Cellularity analyses not available for 3 patients at Month 12 and 1 patient at Month 24; M:E ratio in healthy individuals[1]: 3-4:1

1. Origa R. GeneReviews®. 2018. M:E, myeloid to erythroid ratio; TI, transfusion independence

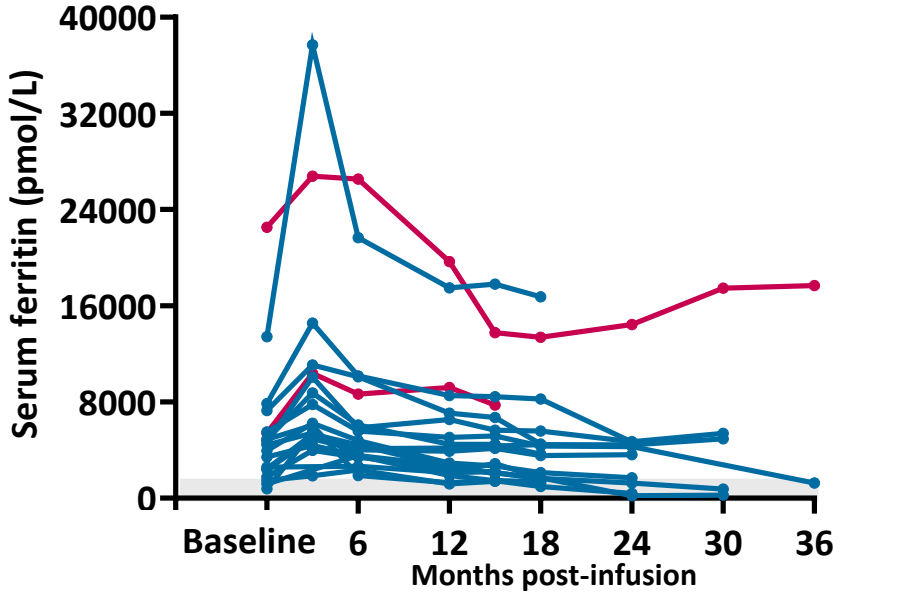
HGB-207: Hepcidin and serum ferritin improved in patients who achieved transfusion independence

- **Iron management after beti-cel treatment**
  - 7/23 patients received phlebotomy for iron reduction
  - 10/23 patients restarted iron chelation therapy after beti-cel infusion including 1 patient who received both phlebotomy and iron chelation
    - 3/10 patients who restarted iron chelation therapy have since stopped chelation
      - Baseline serum ferritin levels in these patients ranged from 2240 – 7849 pmol/L and at last follow-up, ranged from 757 – 4676 pmol/L

Hepcidin



Serum ferritin



Blue lines indicate patient who achieved TI
Red lines indicate patients who were evaluable, but did not achieve TI

Gray bar indicates reference range; TI, transfusion independence

HGB-207 (Northstar-2) Summary

- HGB-207 is a phase 3 study evaluating betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) in patients with transfusion-dependent β-thalassemia (TDT) who have a non-β^0/β^0 genotype
- 89% (17/19) of evaluable patients achieved the primary endpoint of transfusion independence
- Weighted average Hb during TI was 11.9 g/dL, mainly driven by HbA^{T87Q} which stabilizes ~6 months after beti-cel infusion
- Markers of ineffective erythropoiesis improved in patients who achieved transfusion independence
  - Myeloid:erythroid ratio improved and ranged from 1:2.7 to 1.9:1 at Month 12 (N = 16)
  - Soluble transferrin receptor, reticulocytes, and erythropoietin levels are approaching normal levels
- Hepcidin and serum ferritin improved over time and longer follow-up is required to determine whether these measurements normalize
- The treatment regimen had a safety profile generally consistent with the known effects of myeloablation with single-agent busulfan
  - Delayed platelet engraftment was observed, but has not been associated with excess bleeding

Hb, hemoglobin; 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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- Heidi Elliot
- Dana Martin
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- Kimberly Price

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Hannover Medical School, Hannover, Germany

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Ramathibodi Hospital, Mahidol University, Bangkok, Thailand