ASH 2019 Abstract #815

Northstar-3 (HGB-212): Interim results from a phase 3 study evaluating LentiGlobin gene therapy in patients with transfusion-dependent β-thalassemia and either a β^0 or β^+ IVS1-110 (G>A) mutation at both alleles of the *HBB* gene

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Clinical trials of betibeglogene autotemcel gene therapy (beti-cel; LentiGlobin for β-thalassemia)

Phase 1/2 HGB-204 and HGB-205 (N=22)

Transfusion independence with up to 5 years follow-up:

78% (11/14) patients with non-β^0/β^0 genotypes
38% (3/8) patients with β^0/β^0 genotypes

Kwiatkowski JL, et al. ASH 2019. Poster #4628 (tonight's poster session)

Magrin E, et al. ASH 2019. Poster #3358

To improve clinical outcomes, refinements were made to drug product manufacturing

Phase 3 HGB-212 (N=18)
More severe genotypes

β^0/β^0
β^0/IVS1-110
IVS1-110/IVS1-110

Phase 3 HGB-207 (N=23)

90% (9/10) of evaluable patients with non-β^0/β^0 genotypes are transfusion independent

Thompson AA, et al. ASH 2019. Poster #3543 (tonight's poster session)

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

HGB-212

Phase 3 study of betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia)

Key eligibility criteria

- Transfusion-dependent β-thalassemia
- β^0/β^0, IVS1-110/IVS1-110, β^0/IVS1-110
- ≤ 50 years of age

Primary endpoint: Transfusion Reduction

- ≥ 60% reduction in RBC transfusion volume Month 12 – 24

Key secondary endpoint: Transfusion Independence

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

Follow-up: 2 years → long-term follow-up study

Consented
N = 17*

Stem Cell Mobilization Complete
N = 16

Infusion pending
N = 3

beti-cel Infused
N = 13
Target enrollment: 18 patients

Median follow-up:

8.8 months (2.5 – 20.0)

*One patient screen failed due to LIC > 15, but was then successfully rescreened

Hb, hemoglobin; RBC, red blood cell

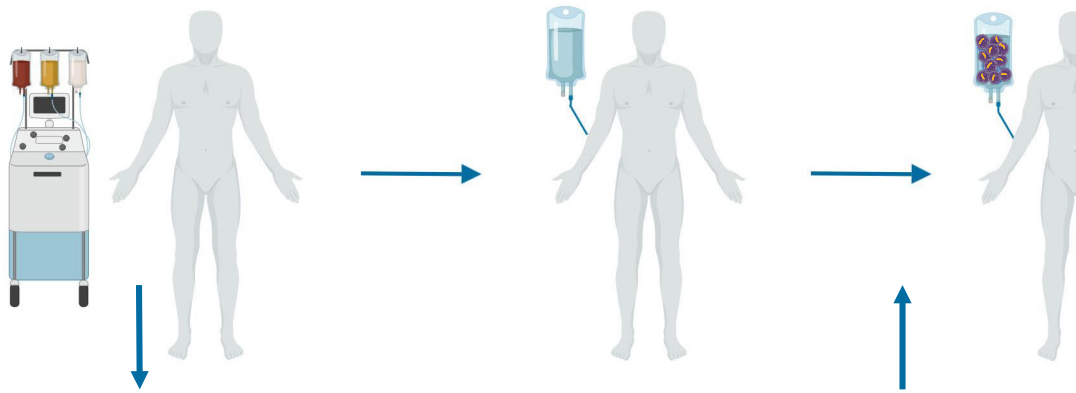
HGB-212: beti-cel gene therapy treatment procedures

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

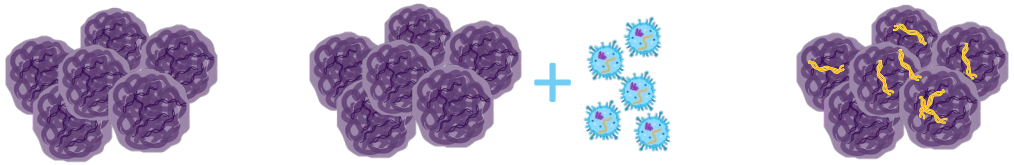
busulfan myeloablative conditioning

beti-cel infusion

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



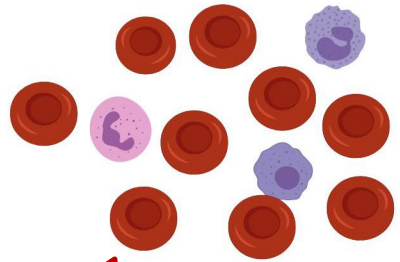
beti-cel centralized manufacturing



Select CD34+ cells

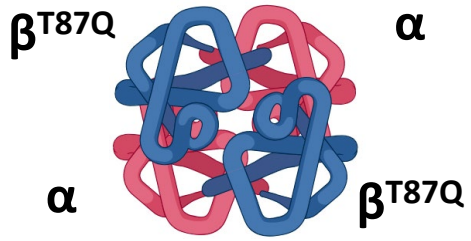
HSCs transduced with BB305 lentiviral vector (encodes for $\beta^{A\text{-}T87Q}$-globin)

Cryopreserve, test, release drug product



HbA^{T87Q}

- Gene-therapy derived functional Hb
- Measurable by HPLC



2-year follow-up

Long-term follow-up study

G-CSF, granulocyte-colony stimulating factor; Hb, hemoglobin; HSC, hematopoietic stem cell; RBC, red blood cell

HGB-212: Patient characteristics

Demographics

		N = 13
Genotypes n (%)	β^0/β^0 IVS1-110/IVS1-110 β^0/IVS1-110	**8** (62) **3** (23) **2** (15)
Male n (%)		**7** (54)
Age at consent, median (min – max), yrs		**17** (7 – 33)
< 12 years, n (%)		**4** (31)
≥ 12 – < 18 years, n (%)		**4** (31)
≥ 18 years, n (%)		**5** (38)
Liver iron concentration median (min – max), mg Fe/g dw		**3.8** (1.2 – 13.2)
Cardiac T2* median (min – max), msec		**39.0** (15.0 – 74.7)
Splenectomy n (%)		**3** (23)

Annualized pre-study pRBC transfusion history

	N = 13 median (min – max)
Transfusion volume mL/kg/yr	**175.5** (74.6 – 276.1)
Number of transfusions n/yr	**17.5** (11.0 – 39.5)
Pre-transfusion Hb g/dL	**9.7** (8.2 – 10.7)

Retrospective data 2 years prior to study enrollment

Patients were enrolled at 3 US and 6 European sites

Hb, hemoglobin; RBC, red blood cell

HGB-212: Treatment characteristics

	N = 13 median (min – max)
Drug product characteristics (per patient)	
Vector copy number, vector copies/diploid genome *Average number of therapeutic gene copies per HSC*	**2.3** (1.2 – 4.3)
CD34+ cells transduced, % *Percentage of HSCs transduced with the BB305 LVV*	**73** (34 – 84)
Cell dose, x 10^6 CD34+ cells/kg	**9.6** (5.9 – 15.8)
Busulfan conditioning	
Estimated daily average AUC over 4 days, µM*min	**4488** (3824 – 9087)
Engraftment	
ANC ≥ 500 cells/µL x 3 days, days	**26** (14 – 38)
Platelets ≥ 20,000 cells/µL, days	**41** (21 – 64)

Target busulfan AUC: q24h: 4200 (min – max: 3800 – 4500) µM*min; q6h: 1050 (min – max: 950 – 1125) µM*min
ANC, absolute neutrophil count; AUC, area under the curve; HSC, hematopoietic stem cell; LVV, lentiviral vector

HGB-212: beti-cel safety profile is generally consistent with myeloablative conditioning with single-agent busulfan

Non-hematologic grade ≥ 3 AEs* *Post-infusion in ≥ 2 patients*	**N = 13 n (%)**
Febrile neutropenia	7 (54)
Stomatitis	5 (38)
Decreased appetite	2 (15)
Mucosal inflammation	2 (15)
Pharyngeal inflammation	2 (15)
AEs considered possibly related to beti-cel by the investigator† *Post-infusion in ≥ 1 patient*	
Abdominal pain	2 (15)
Leukopenia	1 (8)
Neutropenia	1 (8)
Thrombocytopenia (prolonged)	1 (8)

*Hematologic AEs commonly observed post-transplantation have been excluded.
†All were grade 1 or 2.

- Serious AEs:
  - Pyrexia (n=2)
  - Congestive cardiac failure, febrile neutropenia, headache, neutropenia, stomatitis, and thrombocytopenia (all n=1)
- One patient developed serious, grade 3 congestive cardiac failure
  - LVEF fell from 60% to 21% on Day +18, patient was treated and chelation was initiated
  - Patient was asymptomatic after ~4 months; LVEF was 53% and cardiac T2* was 13 msec (baseline 16.6 msec)
  - Investigator reported event was likely related to baseline cardiac iron overload and conditioning

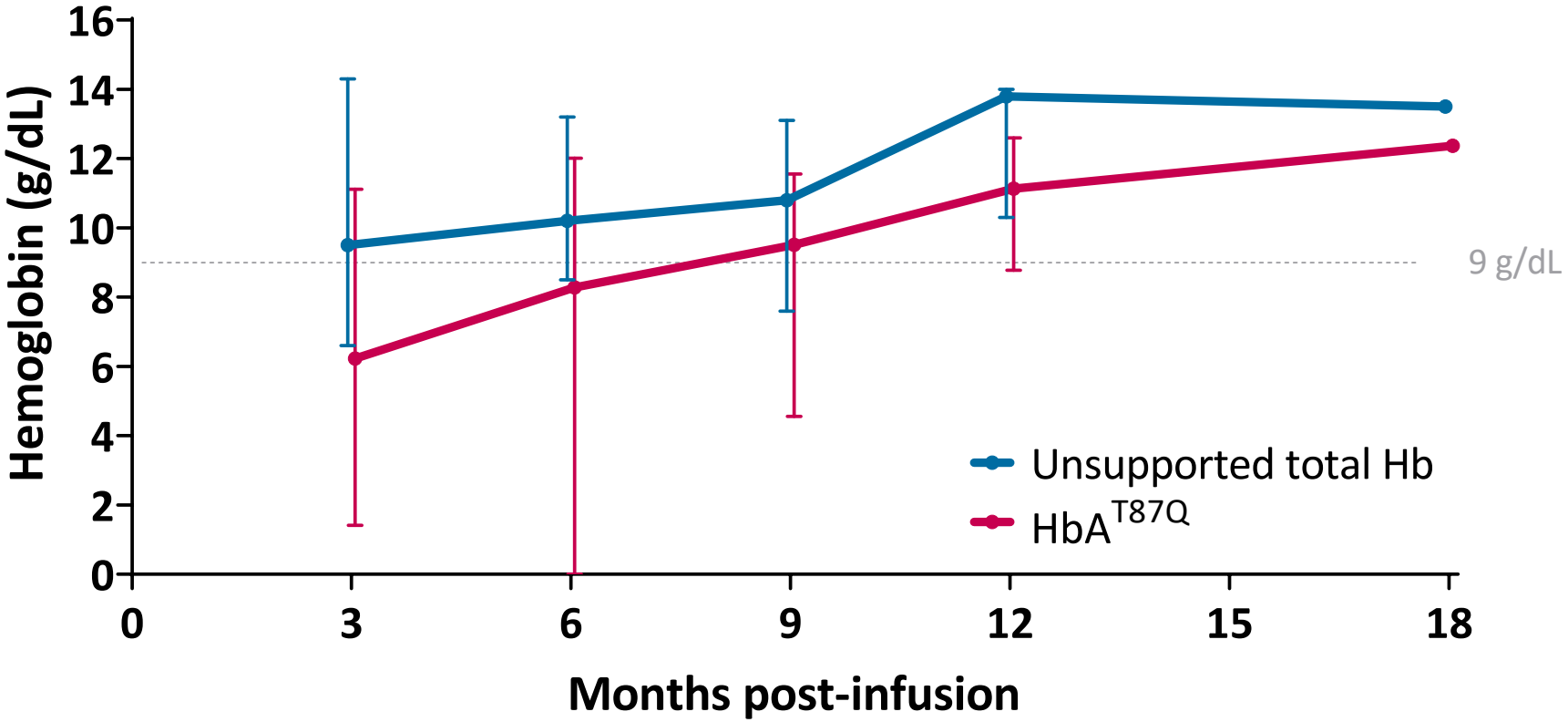
- **No cases of liver veno-occlusive disease**
- **No graft failure or deaths**
- **No complications related to the LVV including replication-competent lentivirus and clonal dominance or malignancy**

AE, adverse event; LVEF, left ventricular ejection fraction; LVV, lentiviral vector

Efficacy Results

HGB-212: Median unsupported total hemoglobin > 10 g/dL at Month 6

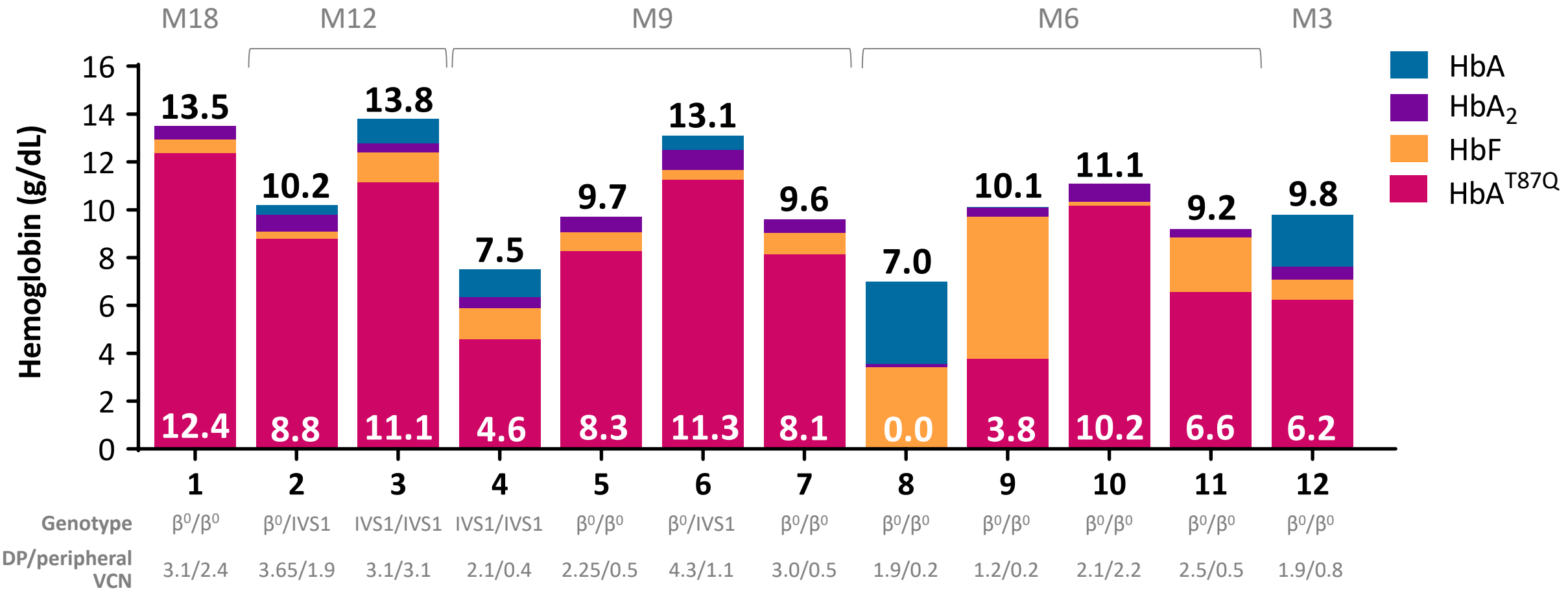
Median (g/dL)	M3	M6	M9	M12	M18
Unsupported total Hb	9.5	10.2	10.8	13.8	13.5
HbA^{T87Q}	6.2	8.3	9.5	11.1	12.4



Unsupported total Hb	8	10	7	3	1
Median HbA^{T87Q}	11	11	7	3	1

Median, min, max depicted; Unsupported total Hb level is defined as Hb without any red blood cell transfusions within 60 days. Hb, hemoglobin

HGB-212: HbA^{T87Q} constitutes the majority of total Hb in most patients ≥ 3 months after treatment

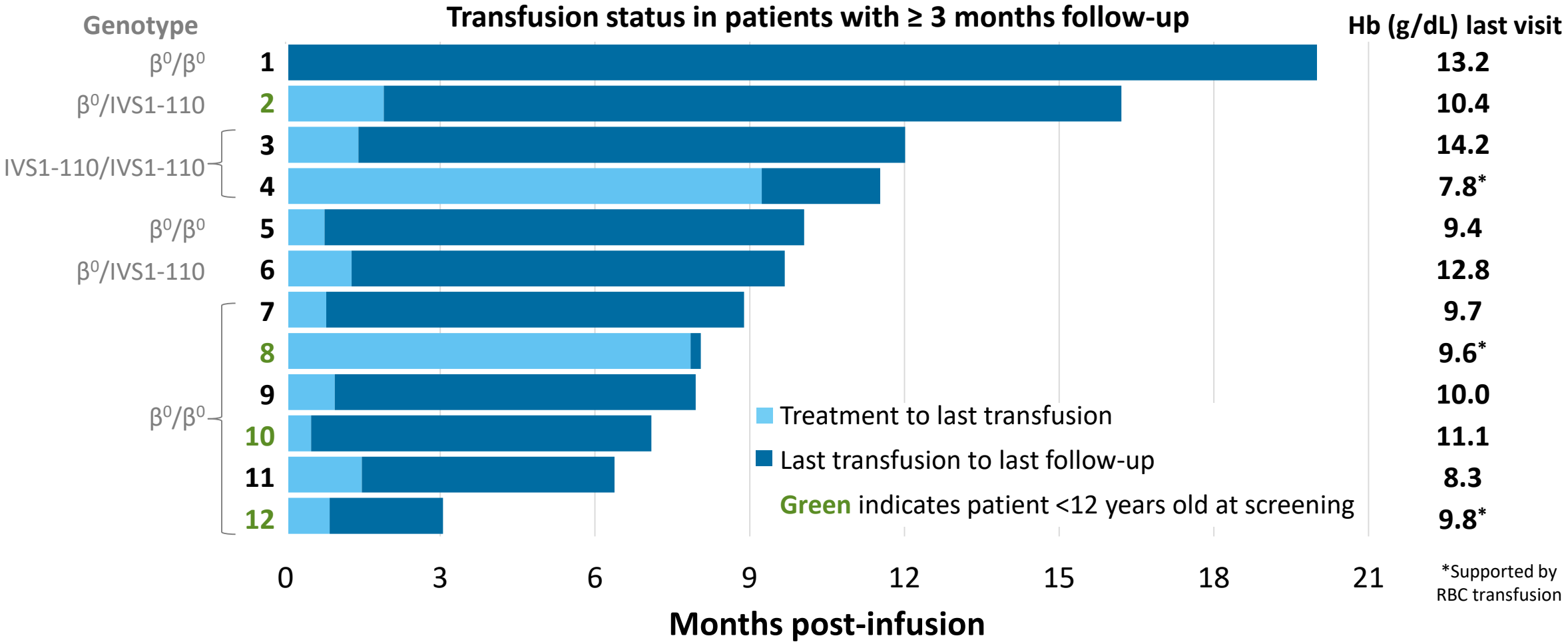


- **9/11 patients with ≥ 6 months follow-up had total Hb > 9 g/dL**
  - One patient who stopped RBC transfusions had high HbF contributing to total Hb
- **3 patients had total Hb > 13 g/dL at last follow-up**

IVS1 = IVS1-110; Hb, hemoglobin; M, month; VCN, vector copy number

Data as of 30 September 2019

HGB-212: 9/11 patients with ≥ 6 months follow-up have been off transfusions for ≥ 3 months



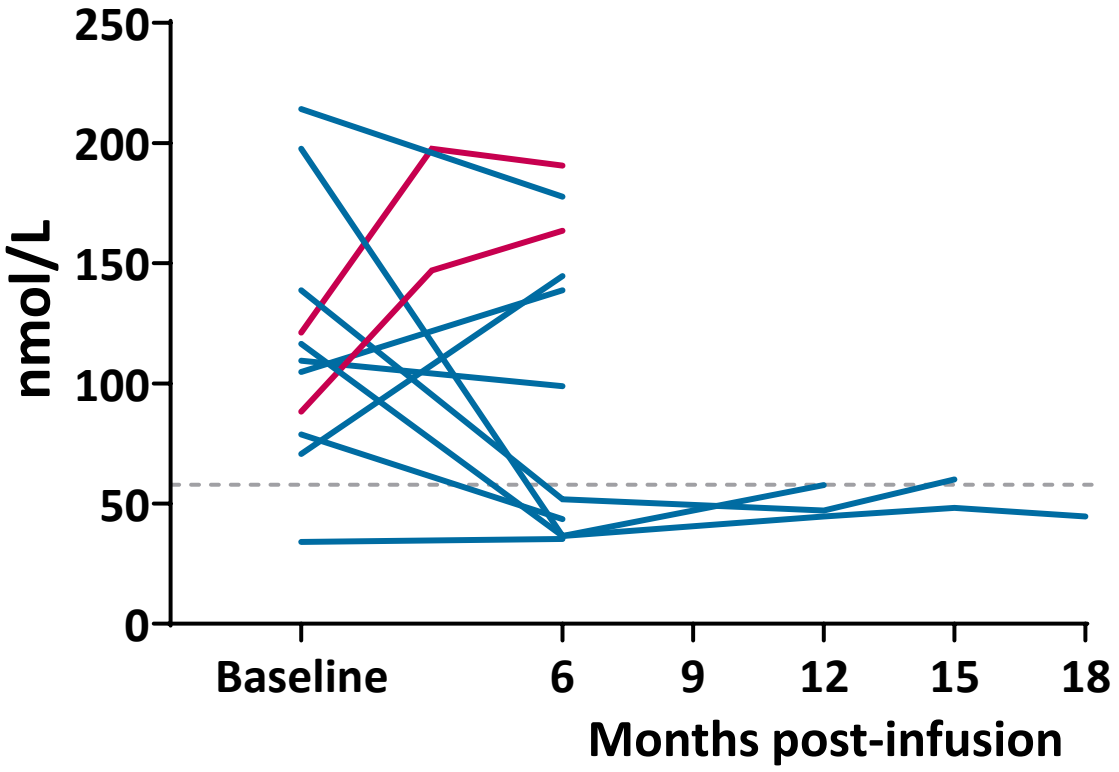
- **Patients 1 and 2 achieved and maintained transfusion independence** Weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months

Hb, hemoglobin; RBC, red blood cell

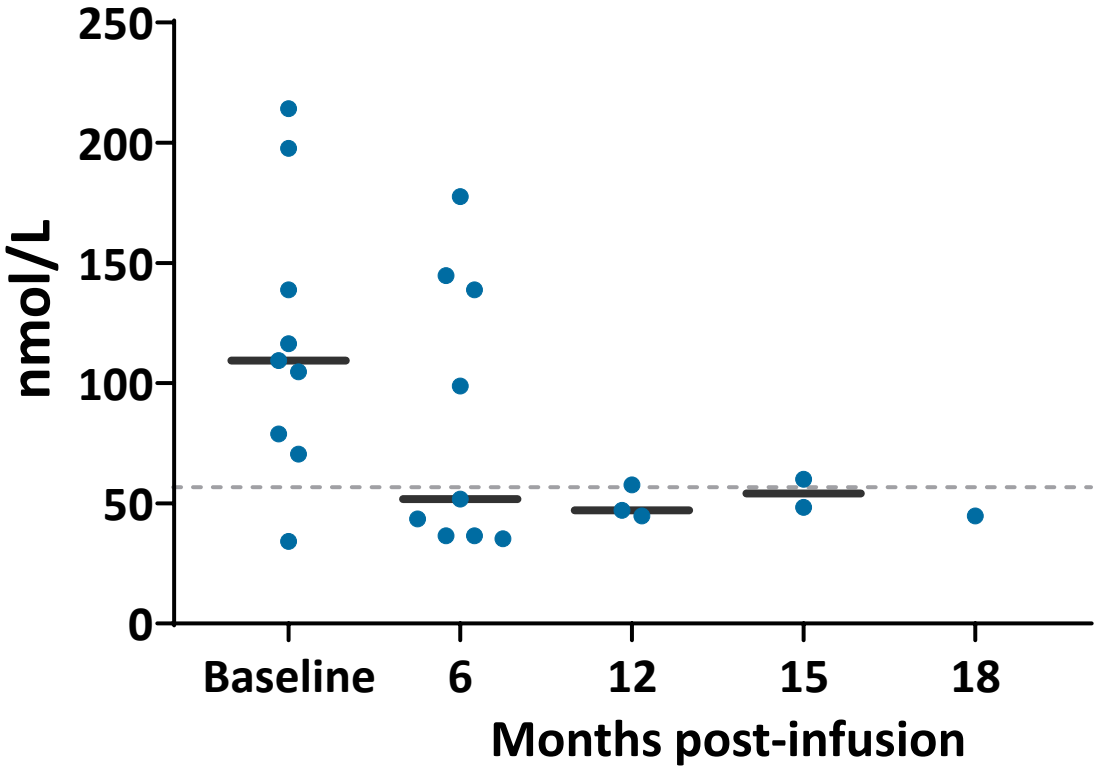
HGB-212: Soluble transferrin receptor in patients with ≥6 months follow-up

Soluble transferrin receptor

Trend in patients with ≥ 6 months follow-up (N=11)



Median values in patients with ≥ 6 months follow-up who discontinued transfusions (N=9)



Red indicates patients still on transfusions
Dotted line indicates upper limit of normal

More data on erythropoietic changes following beti-cel therapy:
Thompson AA, et al. ASH 2019. Poster #3543

HGB-212: Summary of betibeglogene autotemcel gene therapy
(beti-cel; LentiGlobin for β-thalassemia)

- **Interim data suggest that beti-cel enables most patients with transfusion-dependent β-thalassemia (TDT) to produce sufficient HbA^{T87Q} to stop RBC transfusions**
  - Median HbA^{T87Q} at Month 6 was 8.3 g/dL (min – max: 0 – 12.0 g/dL; n=11)
  - 9/11 patients with ≥ 6 months follow-up have been off transfusions for ≥ 3 months
  - 2/2 evaluable patients achieved transfusion independence, including one pediatric patient
    - Weighted average Hb ≥ 9 g/dL without RBC transfusions for ≥ 12 months
- **The safety profile of beti-cel gene therapy was generally consistent with that observed in patients given myeloablative busulfan**
- **Additional follow-up in the HGB-212 study will further clarify the efficacy and safety of beti-cel in patients with TDT and a β^0 or IVS1-110 mutation at both alleles of the *HBB* gene**

Hb, hemoglobin; RBC, red blood cells

Thank you to the study participants and their families

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