# Betibeglogene autotemcel in patients with transfusion-dependent β-thalassemia: Updated results from HGB-207 (Northstar-2) and HGB-212 (Northstar-3)

Franco Locatelli, Janet L. Kwiatkowski, Mark C. Walters, John B. Porter, Suradej Hongeng, Evangelia Yannaki, Andreas E. Kulozik, Martin G. Sauer, Adrian J. Thrasher, Isabelle Thuret, Ashutosh Lal, Ruiting Guo, Weijian Liu, Richard A. Colvin, Alexis A. Thompson

# DISCLOSURES

Amgen (Speakers bureau, advisory board)
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Gilead (Speakers bureau)
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Miltenyi (Speakers bureau)
Neovil (Speakers bureau, advisory board)
Novartis (Advisory board)
Sanofi (Advisory board)

# HGB-207 and HGB-212: Ongoing phase 3 studies of beti-cel

## HGB-207 (Northstar-2)
**non-$\beta^0/\beta^0$ genotypes**

**Primary Endpoint**

**Transfusion Independence**

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

**Additional Key Endpoints**

Hb over time, $\beta^{A\text{-}T87Q}$-globin expression, assessment of improvement in ineffective erythropoiesis

**Enrollment Complete**

**23 patients infused**

**Median follow-up: 24.28 months***

(min – max: 13.0 – 27.5 months)

## HGB-212 (Northstar-3)
**$\beta^0/\beta^0$, $\beta^{+IVS\text{-}I\text{-}110}/\beta^{+IVS\text{-}I\text{-}110}$, and $\beta^0/\beta^{+IVS\text{-}I\text{-}110}$**

**Primary Endpoint**

**Transfusion Independence**

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

**Additional Key Endpoints**

Hb over time, $\beta^{A\text{-}T87Q}$-globin expression, assessment of improvement in ineffective erythropoiesis

**Enrollment Complete**

**18 patients infused**

**Median follow-up: 22.98 months***

(min – max: 4.1 – 26.8 months)

**After completing 2 years of follow-up in HGB-207 and HGB-212, patients are invited to enroll in a 13-year long-term follow-up study, LTF-303**

pRBC, packed red blood cells

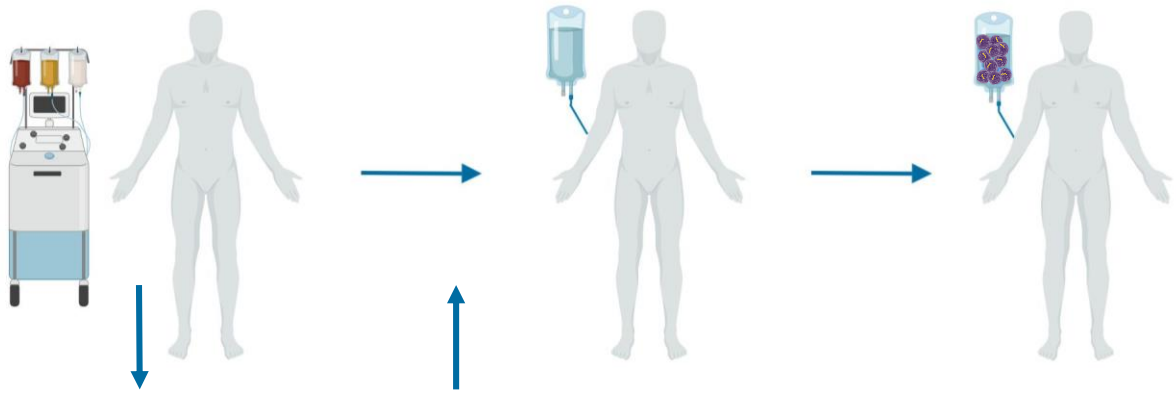
# Treatment procedure of beti-cel clinical studies: One-time *ex vivo* gene addition therapy

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

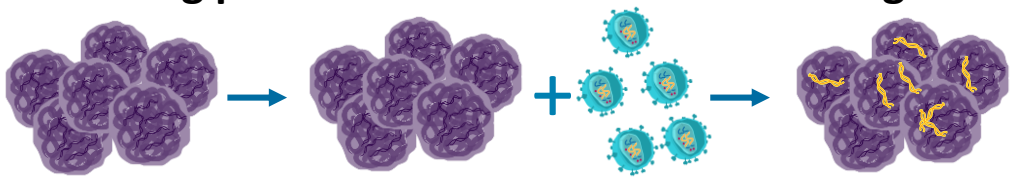
**Busulfan myeloablative conditioning**

**DP infusion**

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



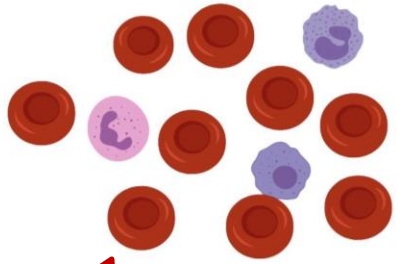
**Drug product centralized manufacturing***



**Select CD34+ cells**

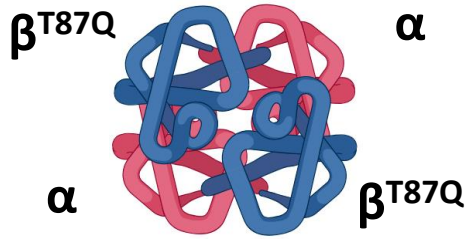
**HSCs transduced with BB305 lentiviral vector (encodes for $\beta^{A\text{-}T87Q}$-globin)**

**Cryopreserve, test, release beti-cel drug product**



**$HbA^{T87Q}$**

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




**2-year follow-up**

**Long-term follow-up study for 13 years**

*HGB-205 was conducted at a single site in France.

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

# HGB-207 and HGB-212: Patient characteristics at enrollment

| Parameters | HGB-207 N = 23 | | HGB-212 N = 18 | |
|---|---|---|---|---|
| **Genotype** n, (%) | $\beta^+/\beta^0$<br>$\beta^E/\beta^0$<br>$\beta^+/\beta^+$ | **12** (52)†<br>**6** (26)<br>**5** (22)‡ | $\beta^0/\beta^0$<br>$\beta^{+IVS1-110}/\beta^{+IVS1-110}$<br>$\beta^0/\beta^{+IVS1-110}$ | **12** (67)<br>**3** (17)<br>**3** (17) |
| **Age at consent,** median (min – max), years | **15** (4 – 34) | | **12.5** (4 – 33) | |
| < 12 years, n (%) | **8** (35) | | **8** (44) | |
| ≥ 12 – < 18 years, n (%) | **6** (26) | | **5** (28) | |
| ≥ 18 years, n (%) | **9** (39) | | **5** (28) | |
| **Liver iron concentration** median (min – max), mg Fe/g dw | **5.3** (1 – 41) | | **3.6** (1 – 13) | |
| **Cardiac T2*** median (min – max), msec | **36.7** (21 – 57) | | **37.0** (15 – 75) | |
| **Splenectomy,** n (%) | **4** (17) | | **3** (17) | |
| **Pre-study transfusion volume^** median (min – max), mL/kg/yr | **207.9** (142 – 274) | | **194** (75 – 289) | |

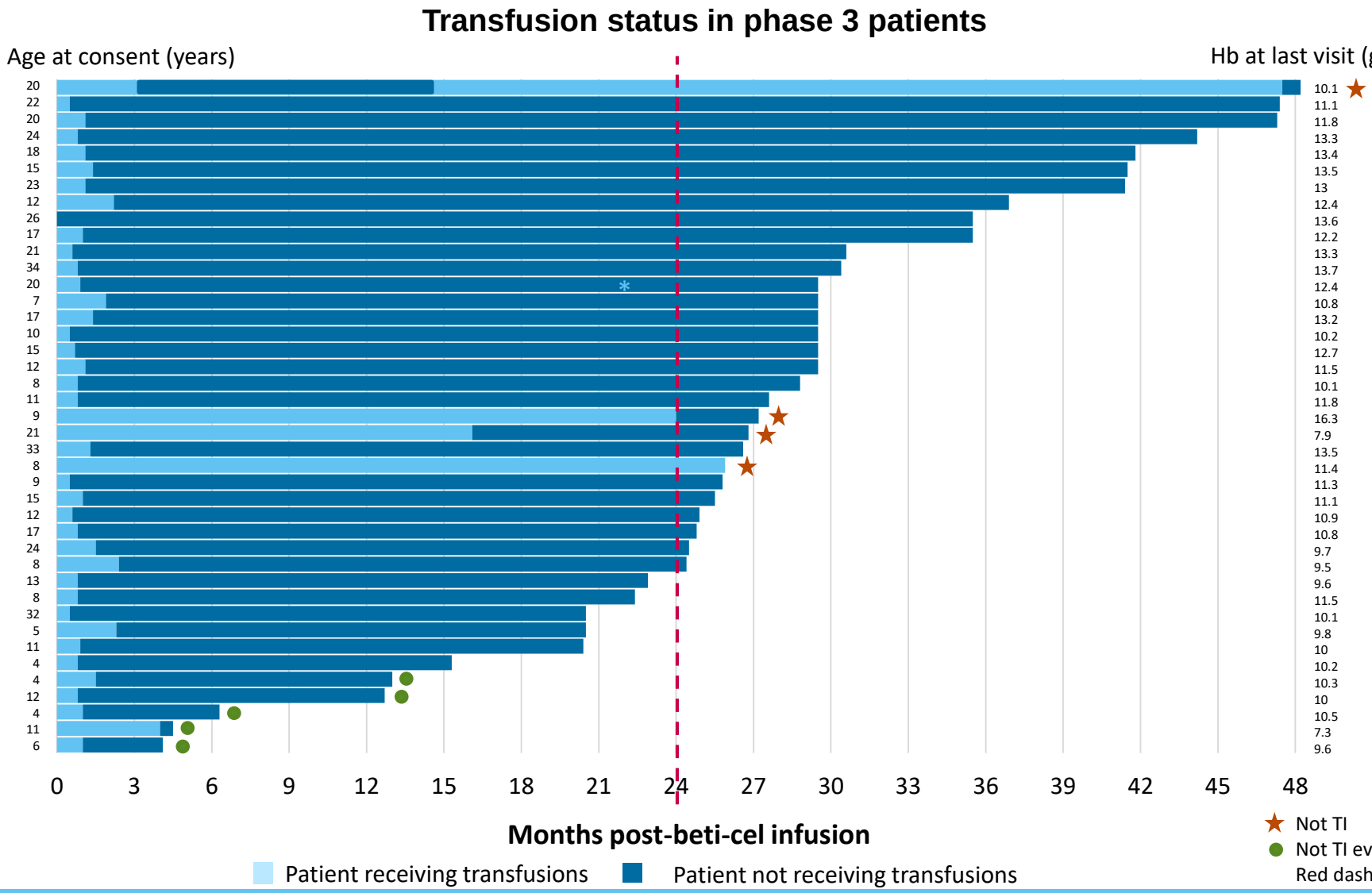
†Includes 2 patients who are heterozygous for the $\beta^+$ IVS1-5 mutation
‡Includes 2 patients who are heterozygous for the $\beta^+$ IVS1-110 mutation and 2 patients homozygous for the $\beta^+$ IVS1-5 mutation
^Annualized retrospective data for 2 years prior to enrollment

# HGB-207 and HGB-212: Drug product and treatment characteristics

| | HGB-207<br>N = 23 | HGB-212<br>N = 18 |
|---|---|---|
| **Drug product characteristics** | median (min – max) | |
| **Vector copy number,** vector copies/diploid genome | **3.0** (2 – 6) | **3.0** (1 – 7) |
| **CD34+ cells transduced,** % | **79.3** (34 – 90) | **78** (34 – 94) |
| **Cell dose,** x $10^6$/kg CD34+ cells | **8.1** (5 – 20) | **10.8** (6 – 42) |
| **Conditioning characteristics**<br>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) | **4237** (3605 – 9086) |
| **Engraftment kinetics** | | |
| **ANC ≥ 500 cells/µL x 3 days,** days | **23** (13 – 32) | **26** (14 – 39) |
| **≥ 20,000 platelets/µL*,** days | **46** (20 – 94) | **49.5** (21 – 64) |
| **Hospitalization** | | |
| **Time from conditioning to discharge,** days | **45** (30 – 92) | **42.5** (29 – 68) |

ANC, absolute neutrophil count; AUC, area under the curve. *Platelet engraftment defined as the first of 3 consecutive platelet count laboratory values ≥20,000/µL obtained on different days, while no platelet transfusions were administered for 7 days immediately preceding and during the evaluation period.

# 89% of evaluable patients in the Phase 3 studies achieved transfusion independence




**89% (32/36) of evaluable patients across both Phase 3 studies achieved the primary endpoint of transfusion independence**

**Weighted average Hb during TI:** 11.6 (9.3 – 13.7) g/dL

**Last pRBC transfusion post-infusion:** 0.85 (0.0 – 2.4) months

**Duration of ongoing TI:** 25 (12.5 – 38.5) months

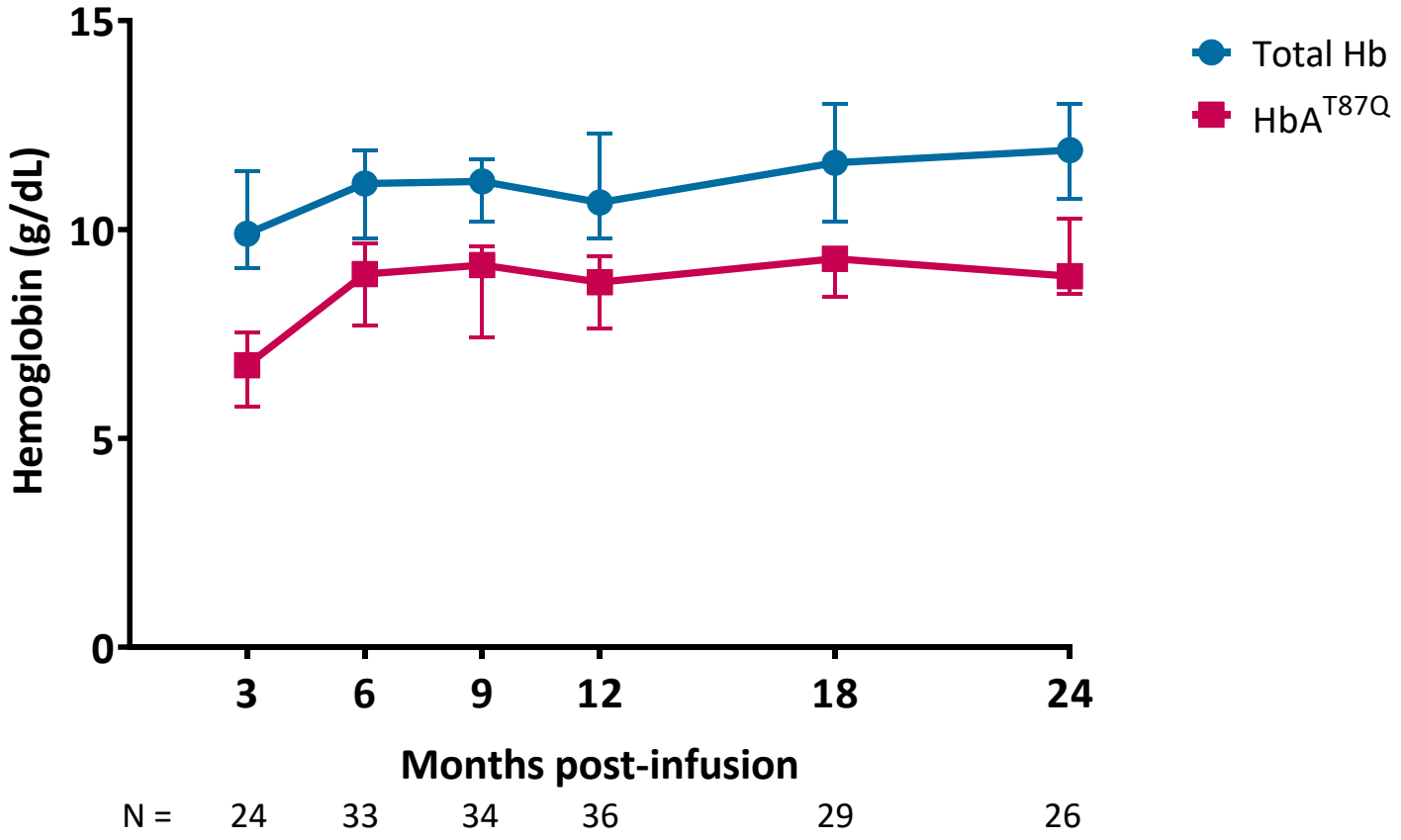
**All patients who achieved TI maintain TI**

*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.
All values are median (min–max). Hb, hemoglobin; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence (defined as weighted average Hb ≥ 9 g/dL without pRBC transfusions for ≥ 12 months)

# Total hemoglobin, mainly driven by gene therapy-derived HbA$^{T87Q}$, stabilizes approximately 6 months post-infusion

## Total unsupported hemoglobin and HbA$^{T87Q}$

| | M3 | M6 | M9 | M12 | M18 | M24 |
|---|---|---|---|---|---|---|
| Total Hb (g/dL) | 9.9 | 10.9 | 11.2 | 10.7 | 11.6 | 11.9 |
| HbA$^{T87Q}$ (g/dL) | 6.6 | 8.8 | 9.2 | 8.7 | 9.3 | 8.9 |



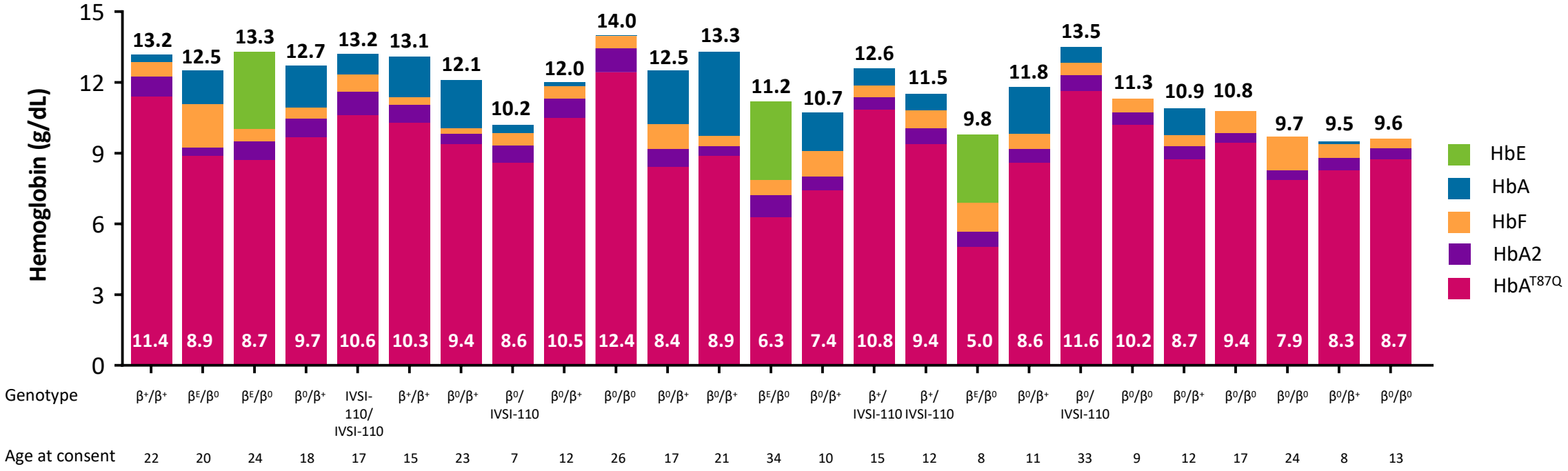

| N = | 24 | 33 | 34 | 36 | 29 | 26 |
|---|---|---|---|---|---|---|

Unsupported is defined as the fraction without any acute or chronic pRBC transfusions within 60 days prior to the measurement date.

Median (Q1, Q3) depicted; Hb, hemoglobin; pRBC, packed red blood cells

# Gene therapy-derived HbA$^{T87Q}$ drives total Hb expression in patients who achieved transfusion independence

## Unsupported hemoglobin fractions at M24 in TI patients with ≥ 24 months follow-up

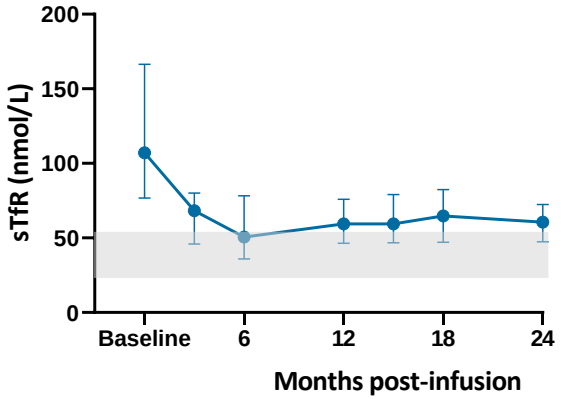



**HbA$^{T87Q}$ contributed to the majority of total Hb (51 – 91%)**

Hb, hemoglobin; TI, transfusion independence. Month 24 data shown.

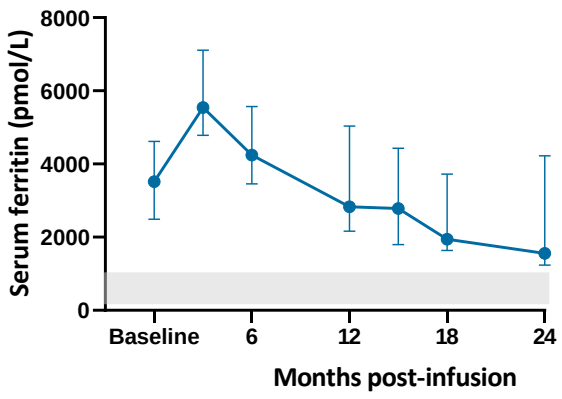
# Biomarkers of ineffective erythropoiesis and iron overload trend towards normal in patients who achieved transfusion independence

## Soluble transferrin receptor (sTfR)



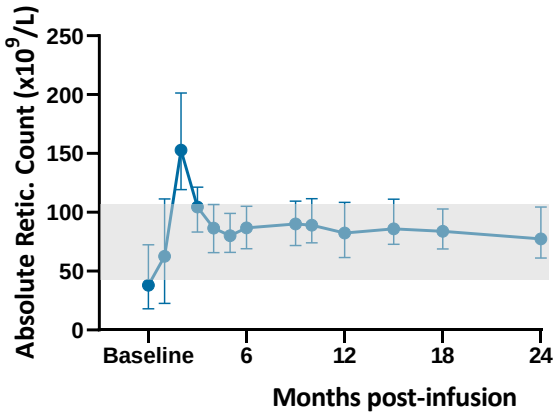

| N = | 32 | 31 | 28 | 29 | 26 |
|---|---|---|---|---|---|

## Serum ferritin



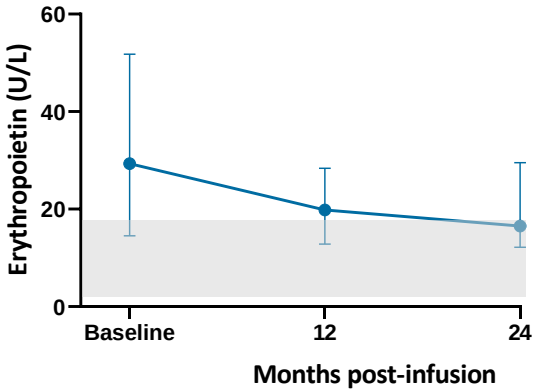

| N = | 32 | 31 | 30 | 30 | 26 |
|---|---|---|---|---|---|

## Absolute reticulocyte count




| N = | 31 | 31 | 30 | 28 | 24 |
|---|---|---|---|---|---|

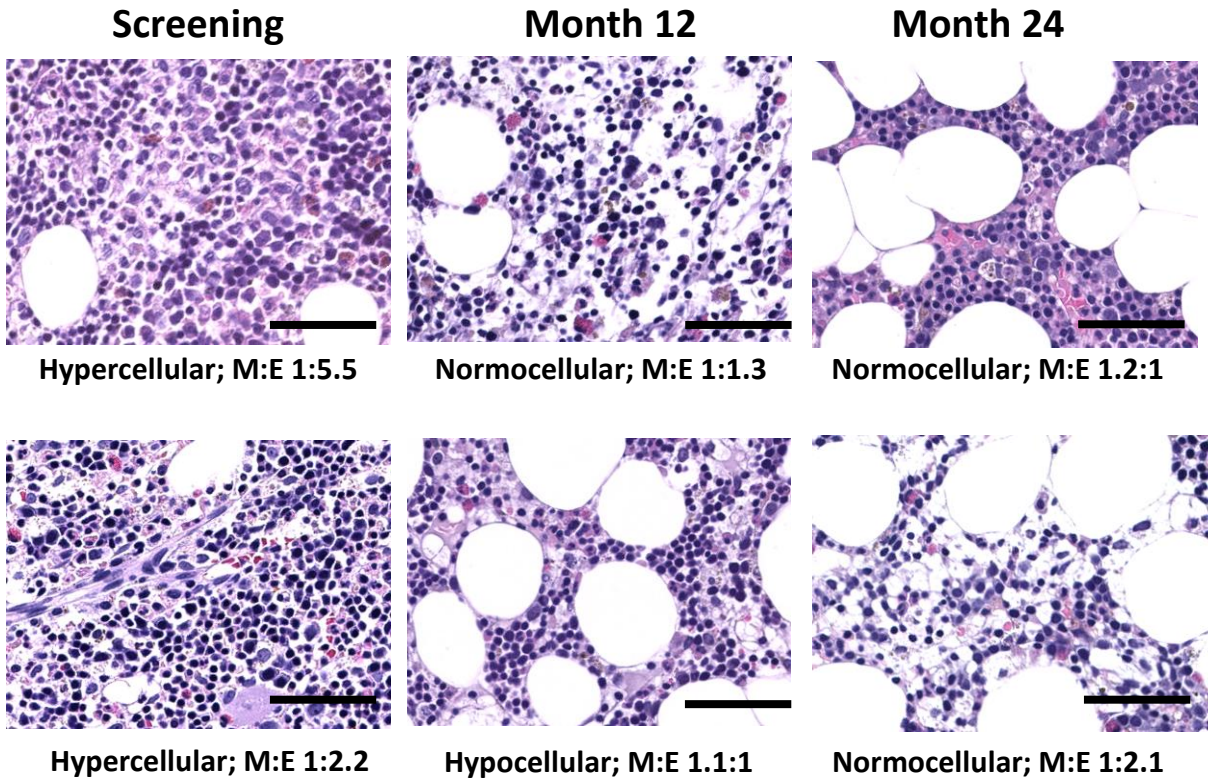
## Erythropoietin



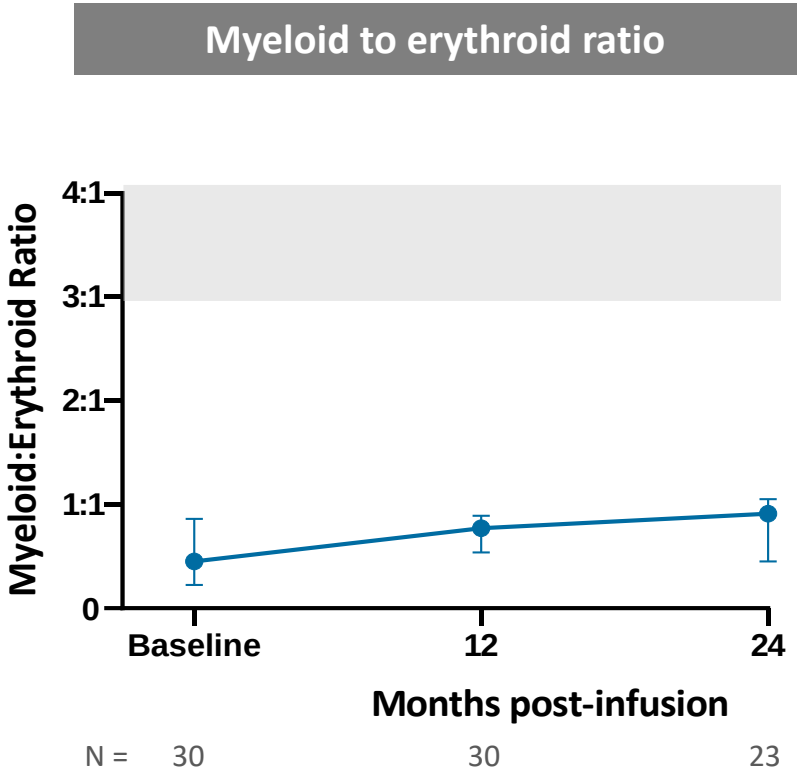

| N = | 27 | 27 | 23 |
|---|---|---|---|

Median (Q1, Q3) depicted; Grey boxes indicate reference ranges (sTfR reference range is for adult patients); sTfR, soluble transferrin receptor

# Bone marrow histology and myeloid to erythroid ratio improved in patients who achieved transfusion independence




**11/20 patients with hypercellular bone marrow at baseline had normocellular histology at last bone marrow assessment after beti-cel gene therapy**



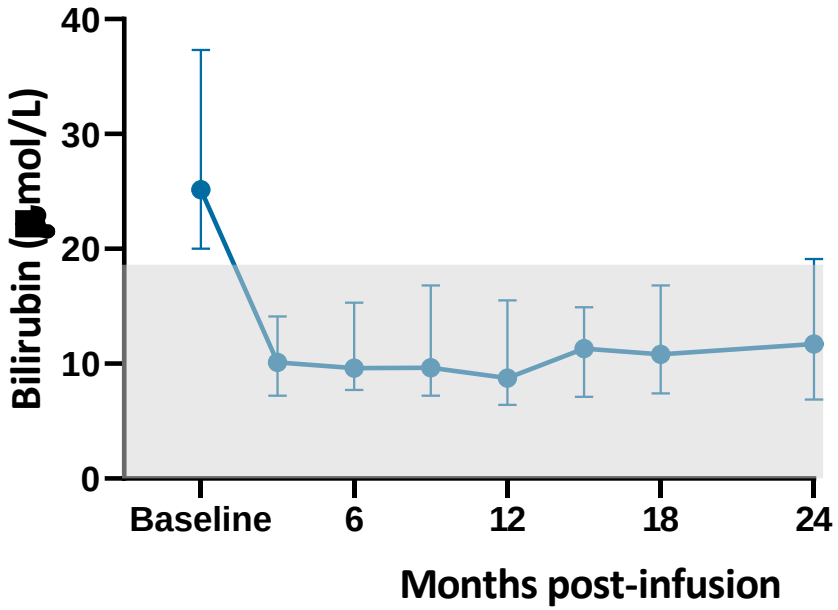

Median (Q1, Q3) depicted
Gray box indicates reference range (may vary with age)

Scale bars: 50 µm.
M:E ratio in healthy individuals[1]: 3-4:1

1. Origa R. GeneReviews®. 2018. M:E, myeloid to erythroid ratio.

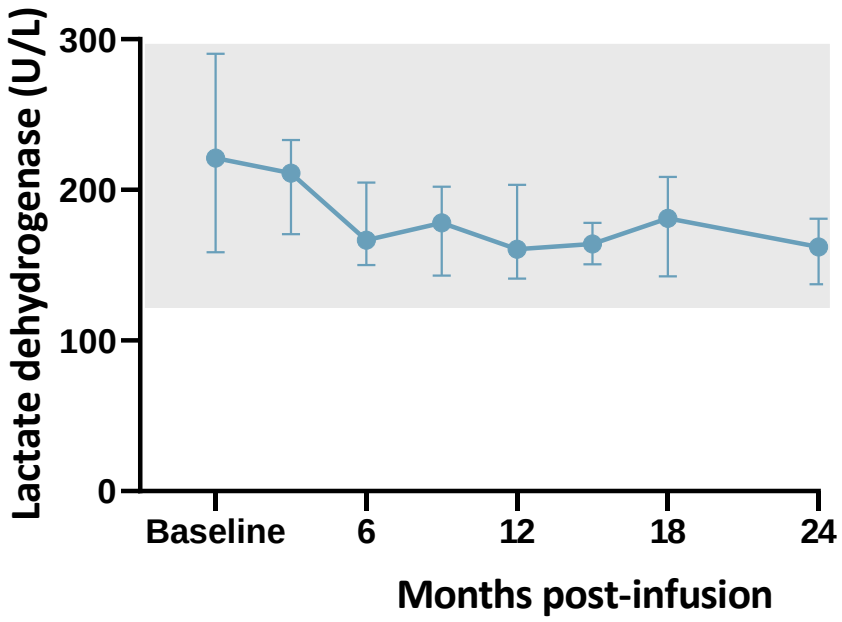
# Hemolysis markers normalize or remain at normal levels in patients who achieved transfusion independence

## Bilirubin




| N = | 32 | 31 | 30 | 31 | 26 |
|---|---|---|---|---|---|

## Lactate dehydrogenase




| N = | 32 | 30 | 30 | 30 | 26 |
|---|---|---|---|---|---|

**Normalization of hemolysis indices suggests healthy red blood cell production in patients who achieved TI**

Median (Q1, Q3) depicted; Grey boxes indicate reference ranges; TI, transfusion independence

# Safety profile generally consistent with that observed in patients given myeloablative busulfan

| **Non-hematologic Grade ≥ 3 AEs*** *Post-beti-cel infusion up to 2-yr follow-up in ≥ 3 patients in either study* | **Phase 3 N = 41 n (%)** |
|---|---|
| Oropharyngeal inflammation | 29 (71) |
| Febrile neutropenia | 20 (49) |
| Epistaxis | 8 (20) |
| Decreased appetite | 6 (15) |
| Pyrexia | 5 (12) |
| Alanine aminotransferase increase | 5 (12) |
| Veno-occlusive liver disease | 3 (7) |
| **Serious AEs** *Post-beti-cel infusion infusion up to 2-yr follow-up in ≥ 2 patients in either study* | |
| Pyrexia | 4 (10) |
| Thrombocytopenia | 3 (7) |
| Veno-occlusive liver disease | 3 (7) |

- Adverse events considered related or possibly related to the drug product were:
  - Thrombocytopenia (n=3), abdominal pain (n=3), leukopenia (n=1), neutropenia (n=1), pain in extremity (n=1), tachycardia (n=1), and autoimmune disorder¥ (n=1). Leukopenia, neutropenia, and one event of thrombocytopenia all occured in the same patient.
  - All events were grade 1/2 except for grade 3 events of autoimmune disorder and 2 events of thrombocytopenia
- VOD occurred in 10% (4/41) of patients
  - VOD severity: Non-serious (grade 2): n=1; Serious (grade 4): n=3
  - All VODs were attributed to busulfan conditioning
  - All VOD resolved with defibrotide treatment
- One patient developed serious, grade 3 CHF unrelated to drug product, which was downgraded to grade 1 at 5 months and resolved at 12 months
- No graft failure, GVHD, or deaths occurred
- No replication-competent lentivirus, clonal predominance, or malignancy detected in any patient (all patients monitored in at least 6-month intervals)

*Hematologic AEs commonly observed post-transplantation have been excluded. ¥Immune thrombocytopenia with autoantibodies to glycoprotein 2b/3a.
AE, adverse event; CHF, congestive heart failure; VOD, veno-occlusive liver disease; GVHD, graft-versus-host disease

# Summary of betibeglogene autotemcel gene therapy

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

## HGB-207 and HGB-212 are phase 3 studies evaluating betibeglogene autotemcel (beti-cel) in patients with transfusion-dependent β-thalassemia (TDT) with genotypes spanning a broad range of TDT severity and across several age groups

### Efficacy

41 patients have been treated with beti-cel in two Phase 3 clinical trials

- Transfusion independence was achieved in 89% (32/36) of evaluable patients
- Median weighted average Hb during TI was 11.6 (9.3 – 13.7) g/dL, mainly driven by $HbA^{T87Q}$ which stabilizes approximately 6 months post-infusion
- Biomarkers of ineffective erythropoiesis trended towards normal over time in patients who achieved transfusion independence
- Hemolysis markers remains within normal ranges in patients who achieved TI despite absence of transfusions

### Safety

The treatment regimen comprising mobilization/apheresis, conditioning, and beti-cel infusion has a safety profile consistent with the known effects of mobilization with G-CSF and plerixafor and myeloablation with single-agent busulfan

- Grade ≥ 3 veno-occlusive liver disease in 3 patients; all resolved with defibrotide
- No graft failure, GVHD, or deaths occurred
- No replication-competent lentivirus, clonal predominance, or malignancy were detected

Data from the long-term follow-up study (LTF-303) of patients who have completed either of the Phase 3 studies are presented in oral presentation S257. Pediatric data from the phase 3 clinical trials are presented in poster EP1301.

Hb, hemoglobin, HSC, hematopoietic stem cell; TI, transfusion independence: weighted average Hb ≥ 9 g/dL without pRBC transfusion ≥ 12 months;
GVHD, graft-versus-host disease

# Thank you to the study participants and their families

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