Mobilization and Apheresis Experience in Patients Receiving One-Time Beti-cel Gene Therapy for Transfusion-Dependent β-Thalassemia: A Pooled Analysis

Jennifer Schneiderman,[1]* David Friedman,[2] Christina Anderson,[3]** Ge Tao,[3] Shamshad Ali,[3] Alexandria Petrusich,[4]** Himal L. Thakar,[3] Richard A. Colvin,[3] Evangelia Yannaki[5]

[1]Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Children's Hospital of Philadelphia, Philadelphia, PA; [3]bluebird bio, Inc., Somerville, MA; [4]Prime Medicine, Inc., Cambridge, MA; [5]G. Papanikolaou General Hospital, Thessaloniki, Greece

**Presenting author. **Former employee of bluebird bio.*

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Betibeglogene autotemcel (beti-cel) gene therapy is approved for the treatment of adult and pediatric patients with TDT[1]

- Beti-cel gene therapy addresses the underlying cause of TDT by adding functional copies of a modified version of the β-globin gene to autologous CD34+ HSCs via a third-generation, self-inactivating lentiviral vector, BB305[2]
- Following one-time beti-cel therapy, HbA^{T87Q}, functional adult Hb containing an amino acid substitution (T→Q) at position 87, is produced in RBCs.[2] HbA^{T87Q} has similar oxygen binding affinity to HbA[3]
- In beti-cel clinical trials, HSC mobilization with G-CSF and plerixafor has been used to achieve sufficient yields of CD34+ cells for gene therapy in patients with TDT (phase 1/2: HGB-204 [NCT01745120] and HGB-205 [NCT02151526]; phase 3: HGB-207 [NCT02906202] and HGB-212 [NCT03207009])[2,4]

This post hoc pooled analysis evaluates data on the mobilization and collection of HSCs from the intent-to-treat populations in the HGB-204, HGB-205, HGB-207, and HGB-212 trials

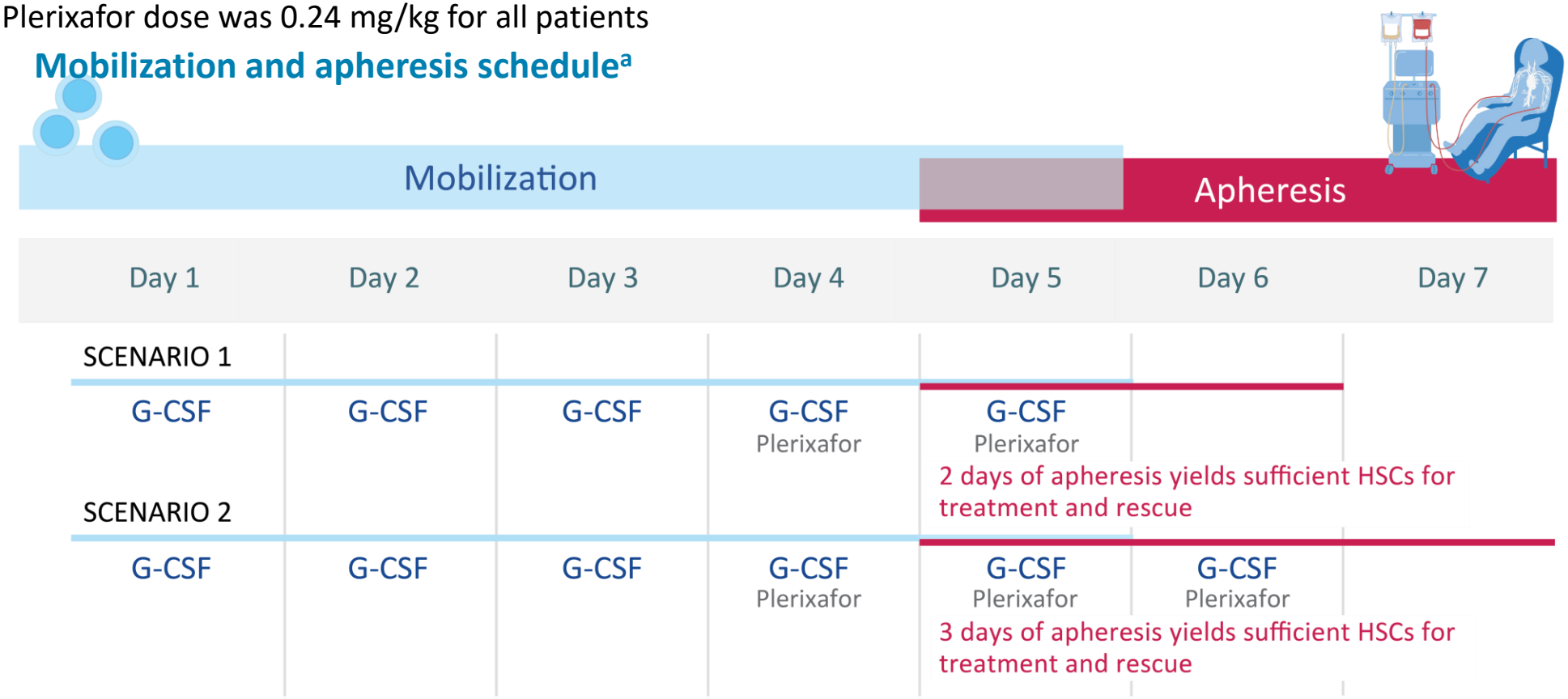
G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HbA, adult hemoglobin; HSC, hematopoietic stem cell; LVV, lentiviral vector; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia.

1. Zynteglo (betibeglogene autotemcel). Prescribing information. bluebird bio, Inc.; 2022. 2. Locatelli F, et al. *N Engl J Med*. 2022;386(5):415-427. 3. Pawliuk R, et al. *Science*. 2001;294(5550):2368-2371.
4. Thompson AA, et al. *N Engl J Med*. 2018;378(16):1479-1493.

Beti-cel trials were single-arm, open-label, single-dose studies that enrolled pediatric and adult patients with TDT, with and without prior splenectomy

- Patients underwent HSC mobilization with G-CSF and plerixafor[a] followed by CD34+ cell collection by apheresis[1,2]
  - G-CSF dose was 5 µg/kg/day in splenectomized patients and 10 µg/kg/day in non-splenectomized patients
  - Plerixafor dose was 0.24 mg/kg for all patients

Mobilization and apheresis schedule[a]



[a]Apheresis generally occurred on mobilization days 5 and 6, and if a third day of collection was needed, G-CSF and plerixafor dosing was extended to day 6.
G-CSF, granulocyte colony-stimulating factor; HSC, hematopoietic stem cell; TDT, transfusion-dependent β-thalassemia.
1. Locatelli F, et al. *N Engl J Med*. 2022;386(5):415-427. 2. Thompson AA, et al. *N Engl J Med*. 2018;378(16):1479-1493.

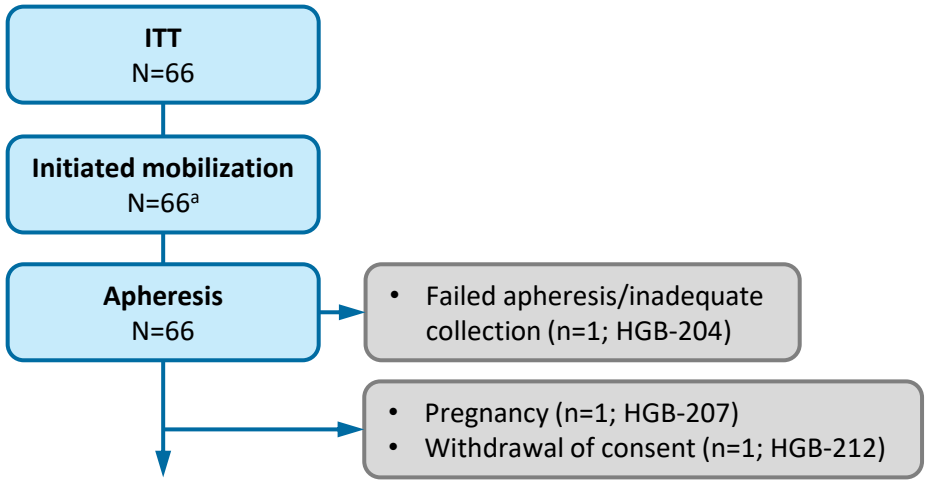
This post hoc analysis evaluates mobilization and collection of HSCs in beti-cel trials

- For a **minimum drug product dose of 5×10^6 CD34+ cells/kg**, the target number of cells to be collected via apheresis (irrespective of age or genotype) was:
  - **$\geq10\times10^6$ CD34+ cells/kg** in HGB-204 and HGB-205
  - **$\geq12\times10^6$ CD34+ cells/kg** in HGB-207 and HGB-212
- The **number of mobilization cycles needed to achieve cell collection target** was analyzed
  - Data for various baseline indexes are summarized descriptively based on number of mobilization cycles
- In an exploratory analysis, Fisher's exact test was used to assess the relationship between **splenectomy status and the number of mobilization cycles**

HSC, hematopoietic stem cell.

Across the 4 beti-cel studies, 66 patients initiated mobilization

Enrollment in beti-cel studies



Patients treated with beti-cel (n=63)			
Phase 1/2		Phase 3	
HGB-204	HGB-205	HGB-207	HGB-212
n=18	n=4	n=23	n=18

Demographic and clinical characteristics

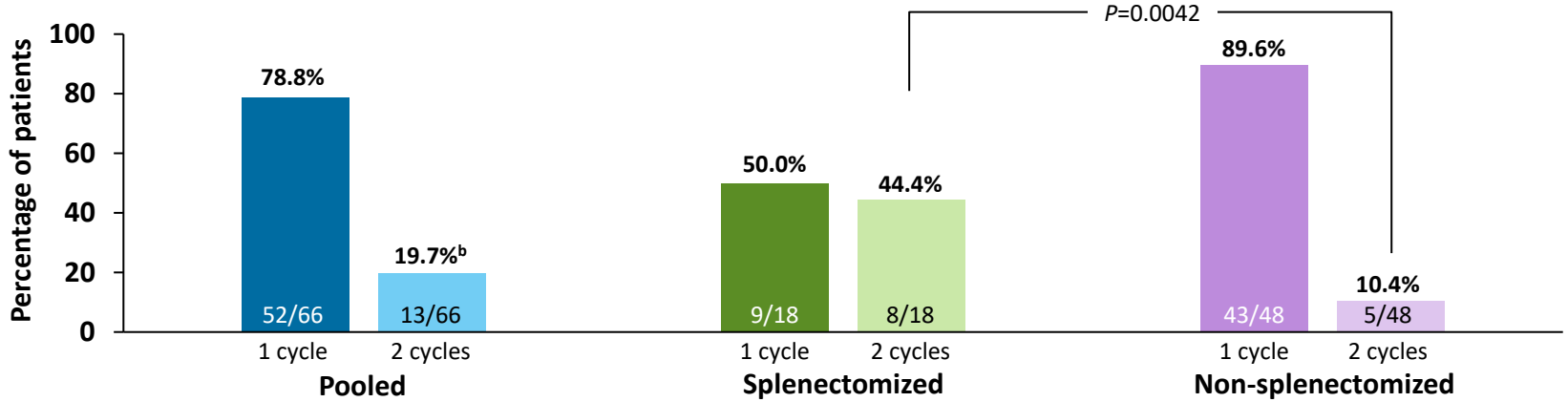
Characteristic	Pooled population N=66	Splenectomized n=18	Non-splenectomized n=48
Age at consent, median (min, max), y	17.5 (4, 35)	21.0 (11, 34)	15.0 (4, 35)
Sex, n (%)			
Female	37 (56.1)	10 (55.6)	27 (56.3)
Male	29 (43.9)	8 (44.4)	21 (43.8)
Genotype, n (%)			
β^0/β^0	21 (31.8)	5 (27.8)	16 (33.3)
Non-β^0/β^0	44 (66.7)	12 (66.7)	32 (66.7)
Other[b]	1 (1.5)	1 (5.6)	0
Weight at initiation of mobilization,[c] median (min, max), kg	49.9 (14.8, 88.1)	60.1 (43.4, 88.1)	40.5 (14.8, 80.4)
pRBC transfusion volume for 2 y before enrollment,[d] median (min, max), mL/kg	190.4 (75, 289)	160.2 (119, 276)	195.0 (75, 289)
Age at initiation of regular transfusions,[e] median (min, max), months	36.0 (1, 312)	48.0 (1, 192)	36.0 (2, 312)

[a]Splenectomized (n=18); non-splenectomized (n=48).[b]Other genotype reported as HBB:c.92+1G>T and unknown. [c]Baseline weight was included if unavailable at initiation of mobilization. [d]Pooled population (n=65); splenectomized (n=17); non-splenectomized (n=48). [e]Pooled population (n=64); splenectomized (n=17); non-splenectomized (n=47). [f]As of March 9, 2021, 63 patients underwent mobilization, apheresis, and beti-cel infusion.
ITT, intent-to-treat; pRBC, packed red blood cells.

In the majority (78.8%) of patients, total cell collection target was achieved in 1 mobilization cycle

- **Total cell collection target was achieved in 1 mobilization cycle in 52/66 (78.8%) patients[a] and after 2 cycles in 13/66 (19.7%)[b]**
  - One patient (HGB-204; 1/66 [1.5%]) with a β^E/β^0 genotype and a prior splenectomy was withdrawn for inadequate cell collection after 1 cycle with G-CSF and plerixafor; this patient experienced leukocytosis and increased lymphocyte counts after baseline that were deemed potentially clinically significant
  - Among phase 3 patients, total cell collection target was achieved after 1 mobilization cycle in 34/43 (79.1%) patients and after 2 cycles in 9/43 (20.9%)
- **A significantly greater proportion of splenectomized patients (8/18 [44.4%]) had 2 mobilization cycles vs non-splenectomized patients (5/48 [10.4%]; *P*=0.0042)**

Number of mobilization and apheresis cycles per patient used for DP

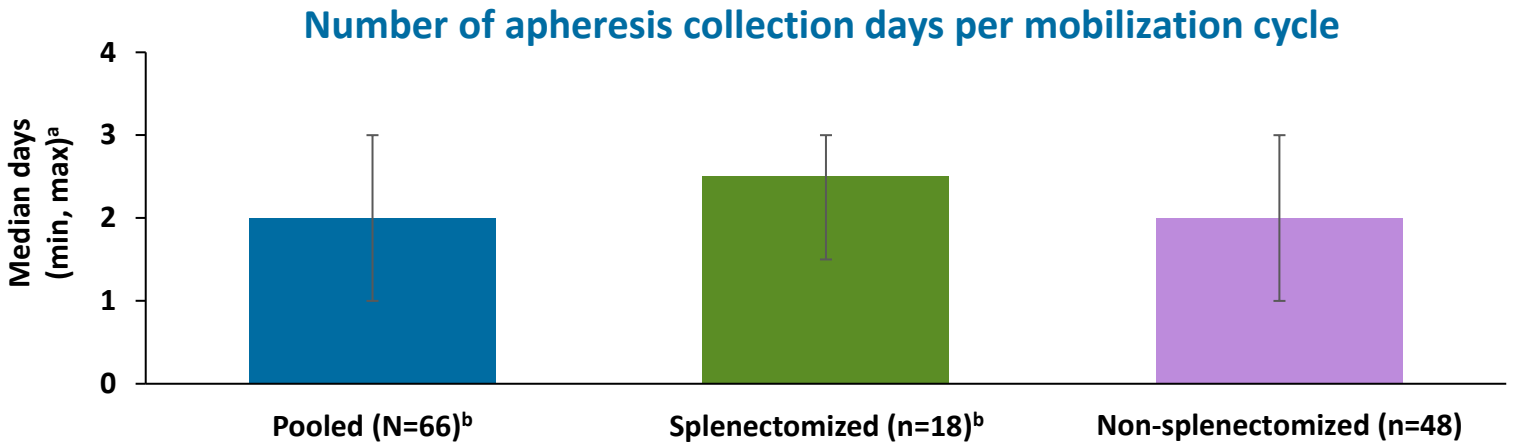


Click here for further details on mobilization cycles and apheresis procedures

[a]The majority of patients (14/16 [87.5%] aged <12 years, 15/17 [88.2%] ≥12 to <18 years, and 23/33 [69.7%] ≥18 years) achieved total cell collection target after 1 mobilization cycle. [b]One patient from HGB-212 (1/66; 1.5%) required 3 mobilization cycles, but cells from only 2 of these cycles were used for DP manufacturing.
DP, drug product; G-CSF, granulocyte colony-stimulating factor.

The median number of apheresis collection days per mobilization cycle was 2.0

- In the pooled population, the median (min, max) number of apheresis collection days per mobilization cycle was **2.0 (1.0, 3.0)**
  - This number was higher in splenectomized patients (2.5 [1.5, 3.0]) than in non-splenectomized patients (2.0 [1.0, 3.0])

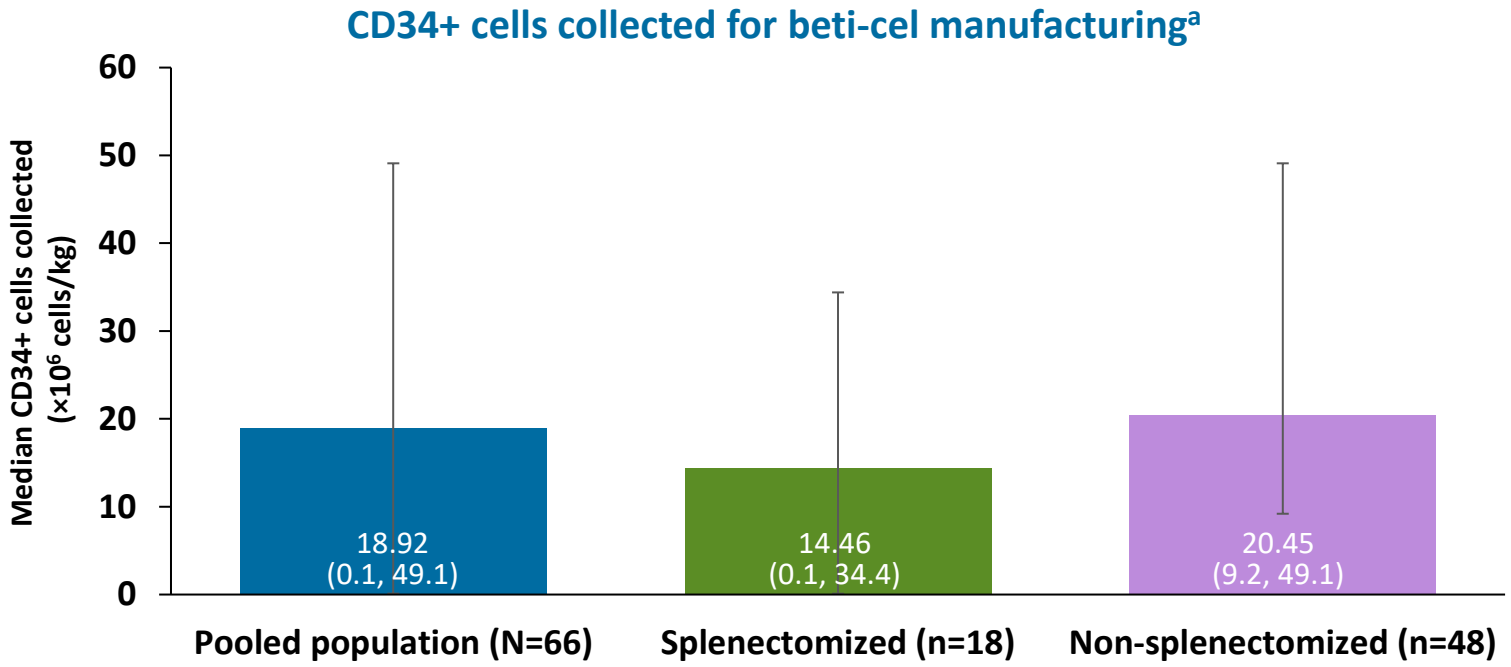


- In the pooled population, **total blood volumes processed**[c] (median [min, max] × [-fold of a patient's total blood volume]) were:
  - 6.32 (2.58, 12.16) for cycle 1 (n=43)
  - 7.05 (1.61, 9.07) for cycle 2 (n=9)

Click here for further details on mobilization cycles and apheresis procedures

[a]Values represent per-patient median number of apheresis collection days, including patients who had 1 mobilization cycle and patients who had 2. [b]Includes 1 patient enrolled in HGB-204 who had inadequate cell collection (CD34+ cell count, 0.1×10^6 cells/kg) despite adequate mobilization (peak peripheral blood CD34+, 162.3 cells/μL) and who was withdrawn after mobilization. This patient had prior splenectomy and experienced leukocytosis and increased lymphocyte counts after mobilization that were deemed potentially clinically significant. [c]Total blood volume was available for 43 patients.

Mobilization/apheresis protocols achieved target CD34+ cell yields for HSC transduction

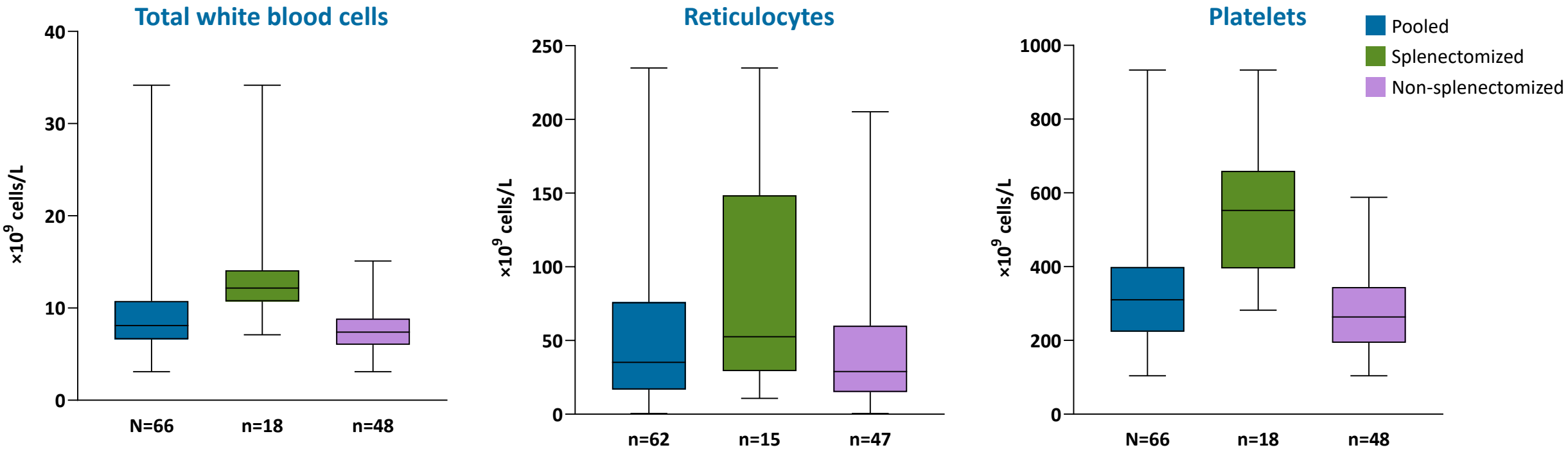


	Pooled population	Splenectomized	Non-splenectomized
Number of CD34+ cells collected for transduction/manufacturing (by Hb[b] prior to start of mobilization), median (min, max), ×10⁶ cells/kg			
Patients with Hb ≥11 g/dL	19.00 (6.35, 49.05); n=42[c]	13.52 (6.35, 33.27); n=11[c]	22.30 (9.50, 49.05); n=31
Patients with Hb <11 g/dL	19.04 (9.20, 34.39); n=23	22.19 (14.10, 34.39); n=6	17.60 (9.20, 33.88); n=17

Click here for further details on CD34+ cell yields

[a]Data presented as median (min, max). [b]To suppress ineffective erythropoiesis and improve red cell rheology for the peripheral blood stem cell harvest, the transfusion regimen was adjusted to maintain Hb ≥10 g/dL within 30 days prior to and during mobilization and apheresis in HGB-204 and to maintain Hb ≥11 g/dL prior to mobilization and apheresis in HGB-205, HGB-207, and HGB-212; in HGB-212, the hypertransfusion scheme lasted at least 60 days prior to and continuing through mobilization and apheresis. [c]Excludes 1 patient enrolled in HGB-204 who had inadequate cell collection (CD34+ cell count, 0.1×10⁶ cells/kg) despite adequate mobilization (peak peripheral blood CD34+, 162.3 cells/µL) and who was withdrawn after mobilization. This patient had prior splenectomy and experienced leukocytosis and increased lymphocyte counts after mobilization that were deemed potentially clinically significant.
Hb, hemoglobin; HSC, hematopoietic stem cell.

Median WBCs, reticulocytes, and platelet counts at baseline were higher in splenectomized patients



- Among patients with available values, baseline median liver iron concentration, Hb, total WBCs, neutrophil:lymphocyte ratio in blood, and myeloid:erythroid ratio in bone marrow were similar between patients who had 1 mobilization cycle and those who had 2

Click here for further details on baseline characteristics of key laboratory data

Hb, hemoglobin; WBC, white blood cell.

The mobilization and apheresis protocols were well tolerated

	Pooled population N=66	Splenectomized n=18	Non-splenectomized n=48
Patients with AEs attributed to mobilization/apheresis, n (%)	51 (77.3)	16 (88.9)	35 (72.9)
AEs in >1 patient			
Hypocalcemia	13 (19.7)	3 (16.7)	10 (20.8)
Thrombocytopenia	12 (18.2)	5 (27.8)	7 (14.6)
Bone pain	10 (15.2)	1 (5.6)	9 (18.8)
Headache	9 (13.6)	3 (16.7)	6 (12.5)
Back pain	6 (9.1)	1 (5.6)	5 (10.4)
Peripheral sensory neuropathy	6 (9.1)	4 (22.2)	2 (4.2)
Nausea	5 (7.6)	1 (5.6)	4 (8.3)
Dizziness	4 (6.1)	3 (16.7)	1 (2.1)
Leukocytosis[a]	4 (6.1)	2 (11.1)	2 (4.2)
Patients with grade ≥3 AEs attributed to mobilization/apheresis, n (%)	7 (10.6)	4 (22.2)	3 (6.3)
Thrombocytopenia	5 (7.6)	3 (16.7)	2 (4.2)
Leukocytosis[a]	2 (3.0)	1 (5.6)	1 (2.1)
Pain	1 (1.5)	1 (5.6)	0
Hypocalcemia	1 (1.5)	1 (5.6)	0
Hypokalemia	1 (1.5)	0	1 (2.1)
Patients with SAEs attributed to mobilization/apheresis, n (%)	1 (1.5)	1 (5.6)	0
Thrombocytopenia	1 (1.5)	1 (5.6)	0
Hypokalemia	1 (1.5)	1 (5.6)	0

- Overall, 77.3% (51/66) of patients experienced ≥1 AE attributed to mobilization/apheresis
- The most common AEs attributed to mobilization/apheresis were hypocalcemia and thrombocytopenia
- Grade ≥3 AEs occurred in 22.2% (4/18) of splenectomized patients vs 6.3% (3/48) of non-splenectomized patients
- SAEs (thrombocytopenia and hypokalemia) were reported in only 1 patient
  - This patient had a prior splenectomy

[a]Leukocytosis occurred in 2 patients in HGB-207: 1 patient had a maximum leukocyte count of 104.12×10^9 cells/L and 1 patient had a maximum leukocyte count of 118.05×10^9 cells/L.
AE, adverse event; SAE, serious adverse event.

Conclusions

- The mobilization and apheresis protocols used in beti-cel clinical trials for the treatment of patients with TDT **were effective for achieving target CD34+ cell yields** for HSC transduction
  - The **majority of patients** in the pooled trial population **achieved collection target with only 1 mobilization cycle**
- The proportion of splenectomized patients who had 2 mobilization cycles was significantly greater compared with non-splenectomized patients
- **The mobilization and apheresis protocols were well tolerated**, with hypocalcemia and thrombocytopenia being the most common AEs attributed to mobilization and apheresis
- These analyses can inform real-world practice to achieve optimal CD34+ cell yields for successful beti-cel drug product manufacturing and treatment

AE, adverse event; HSC, hematopoietic stem cell; TDT, transfusion-dependent β-thalassemia.

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