Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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BLA 125717

Betibeglogene autotemcel (beti-cel)

Treatment of patients with β-thalassemia who require regular red blood cell (RBC) transfusions

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Outline

- Beta-thalassemia and current therapy
- Sources of efficacy and safety data in BLA 125717
- Presentation of efficacy
- Presentation of safety
  - Special safety concerns
- Benefit-Risk

β-thalassemia

- Hemoglobinopathies due to hemoglobin subunit beta (*HBB*) gene mutations which impair β-globin production leads to:
  - Severe anemia, lifelong transfusion-dependence
  - Iron overload, life-threatening comorbidities (endocrinopathies, cardiomyopathy, cirrhosis)
  - Decreased survival
- Transfusion Dependent Thalassemia (TDT):
  - The most severe phenotype
  - Mortality up to 80% by age 5, without RBC transfusions

Treatment Options

- Supportive Care
  - Regular RBC transfusions
  - Iron chelation
- Luspatercept: chronic treatment to reduce transfusion burden
- Allogeneic hematopoietic stem cell transplantation (AHSCT)
  - > 85% disease-free survival in children and 65% in adults
  - < 25% of patients have an HLA-matched sibling donor
- Therefore, unmet medical need

Betibeglogene autotemcel (beti-cel)

- Autologous hematopoietic stem cells (HSCs) transduced with BB305 lentiviral vector (LVV) encoding βA-T87Q-globin

- βA-T87Q-globin
  - Variant β-globin, designed to bind to α-globin
  - Reconstitutes production of stable, functional hemoglobin in RBCs

- Goal of therapy
  - Enhance production of RBCs
  - Transfusion-independence

Studies Reviewed in BLA 125717

Study/ Age / Genotype	Study and Design	Product Generation/ Dosage	Number of Subjects
HGB–204 ≥ 12 to ≤ 35 years All genotypes	Phase 1/2 Single-arm, open label, multi-site, single dose	(Generation 1) ≥ 3×10^6 CD34+ cells/kg	19 enrolled 18 treated Completed: Feb 2018
HGB-207 Cohort 1: ≥ 12 to ≤ 50 years Cohort 2: <12 years old Non-β0/β0	Phase 3 Single-arm, open label, multi-site, single dose	(Generation 2) ≥ 5×10^6 CD34+ cells/kg	24 mobilized 23 treated Start: 2016 Ongoing
HGB-212 ≤ 50 years β0/β0, IVS-I-110/IVS-I-110 & β0/IVS-I-110	Phase 3 Single-arm, open label, multi-site, single dose	(Generation 2) ≥ 5×10^6 CD34+ cells/kg	19 mobilized 18 treated Start: 2017 Ongoing
LTF-303 Any age All genotypes	Non-interventional long-term safety follow up study	Not applicable	47 enrolled Start: 2014 Ongoing

Source: Excerpted from Applicant's Summary of Clinical Efficacy Document, Table 1.

Study Design: HGB-207 and HGB-212

Open-label, single-arm, multicenter, with four stages:

1. Screening via detailed history of TDT management
2. Apheresis after mobilization with G-CSF / plerixafor to collect HSPCs for beti-cel manufacture
3. Myeloablation with busulfan, followed by beti-cel infusion on Day 1
4. Follow-up to Month 24

HGB-207 & HGB-212 Key Inclusion Criteria

- Age ≤ 50 years old
- TDT with history of ≥ 100 mL/kg/year of RBC transfused in 2 years preceding enrollment
- Subjects ≥ 12 years could also be managed under standard thalassemia guidelines with ≥ 8 RBC transfusions per year in 2 years preceding enrollment

HGB-207 and HGB-212 Exclusion Criteria

- Study HGB-207 excluded:
  - β0 mutation present on both *HBB* alleles
  - Functionally severe IVS I-110 (G→A) [HGVS nomenclature] *HBB*: c.93-21G>A] considered equivalent to β0 mutation)

- Study HGB-212 excluded:
  - Any mutation other than β0 (e.g., β+, βE, βC) on *HBB* allele

HGB-207 and HGB-212 Exclusion Criteria

- Positive test for HIV, hepatitis B, C, or syphilis
- Clinically significant bacterial, viral, fungal, or parasitic infection
- WBC < 3×10^9/L, and/or platelets <100×10^9/L
- History of malignancy or immunodeficiency disorder
- Familial Cancer Syndrome in immediate family
- Severe organ impairment
- Uncorrected bleeding disorder

Phase 3 Study Efficacy Endpoints

Primary:

- Proportion of subjects with transfusion-independence (TI), defined as weighted average hemoglobin (Hb) ≥9 g/dL without any RBC transfusions for a continuous period of ≥ 12 months at any time during the study after beti-cel infusion

Secondary:

- Duration of TI; proportion with TI at Month 24; time from beti-cel infusion to achievement of TI, and weighted average Hb during TI
- Characterization of transfusion reduction; weighted average nadir Hb prior to enrollment vs. that from Month 12 to 24; evaluate unsupported Hb levels over time
- Assess liver and cardiac iron burden, quality of life and chelation

Study Safety Assessments

- Success and kinetics of stem cell engraftment
- Transplant-related mortality to Day 100 and Day 365
- Overall Survival
- Detection of vector-derived RCL
- Monitoring of laboratory parameters
- Frequency and severity of clinical adverse events
- Assessment of insertional oncogenesis

Phase 3 Studies: Disposition

Parameter	Statistic	HGB207	HGB212	Total
Signed Informed Consent Form (ICF)	N	32	19	51
Screening failed	n (%)	5 (16)	0	5 (10)
Withdrew consent before mobilization	n (%)	3 (9)	0	3 (5)
Received Mobilization	n (%)	24 (75)	19 (100)	43 (84)
Received beti-cel infusion (Efficacy Analysis Population)	n (%)	23 (72)	18 (95)	41 (80)

Source: Reviewer calculations from PDISE ADSL dataset

Phase 3 Studies: Demographics

Age

Parameter	Statistic	HGB207 N=23	HGB212 N=18
Age at ICF or assent (years)	Median Min, Max	15 3,34	12.5 4,33
<12	n (%)	8 (35)	8 (44)
≥12 to <18	n (%)	6 (26)	5 (28)
≥18	n (%)	9 (39)	5 (28)

Genotype

Parameter	Statistic	HGB207 N=23	HGB212 N=18
β0/β0	n (%)	0	12 (67)
Non-β0/β0	n (%)	23 (100)	6 (33)

Sex

Parameter	Statistic	HGB207 (N=23)	HGB212 (N=18)	Phase 3 Total (N=41)
Male Sex	n (%)	11 (48)	10 (56)	21 (51)
Female Sex	n (%)	12 (52)	8 (44)	20 (49)

Source: Reviewer calculations from PDISE ADSL dataset

Key Baseline Characteristics

Parameter	Statistic	HGB-207 N=23	HGB-212 N=18	Phase 3 N=41
HBB Genotype β0/β0 βE/β0 β0/β+ βE/β+ β+/β+ Other	n (%) n (%) n (%) n (%) n (%) n (%)	0 6 (26) 12 (52) 0 5 (22) 0	12 (67) 0 3 (17) 0 3 (17) 0	12 (29) 6 (15) 15 (37) 0 8 (19) 0
Baseline annualized transfusion volume (mL/Kg/year)	Median Min, Max	208 142, 274	194 75, 289	198 75, 289
Baseline weighted average nadir Hb (g/dL)	Median Min, Max	9.6 7.5, 11	9.5 8, 11	9.6 7.5, 11

Source: ADSL dataset

Results: Primary Efficacy Analysis
Transfusion-Independence (TI)

Parameter	Statistic	HGB-207 Cohort 1 (≥12 years old) (N=15)	HGB-207 Cohort 2 (<12-year-old) (N=8)	HGB-212 (N=18)	Phase 3 Total (N=41)
TI-evaluable	N	15	7	14	36
Subjects with TI at any time	n (%) 2-sided 95% CI	14 (93) (68,100)	6 (86) (42, 100)	12 (86) (57, 98)	32 (89) (74, 97)

Source: Reviewer calculations from PDISE-ADEF2 dataset

Secondary Efficacy Endpoints

Parameter	Statistic	Total (N=32)
Subjects with TI at Month 24[a]	n/N (%)	27/31 (87)
Subjects with TI at Month 36[a]	n/N (%)	9/10 (90)
Subjects with TI Last follow-up[a]	n/N (%)	32/36 (89)
Observed duration of TI (months)	Median (range)	26 13, 39
Weighted average Hb during TI (g/dL)	Median (range)	11.5 9.3, 13.7
Time from beti-cel infusion to last transfusion prior to TI (months)	Median (range)	0.8 0.0, 2.4
Time from beti-cel infusion to achievement of TI (months)	Median (range)	16 15, 25

Source: Reviewer analysis of PDISE ADEF2 dataset. [a]The denominator is based on the number of subjects reaching the noted Month visit.

Efficacy Conclusion

- Beti-cel treatment led to TI in 89% of subjects
- Median time from beti-cel infusion to last RBC transfusion 0.8 months
- Median observed duration of TI of 26 months (range 13-39)

Safety

- Safety analysis population (N=59)
  - HGB-204 (N=18)
  - HGB-207 (N=23)
  - HGB-212 (N=18)

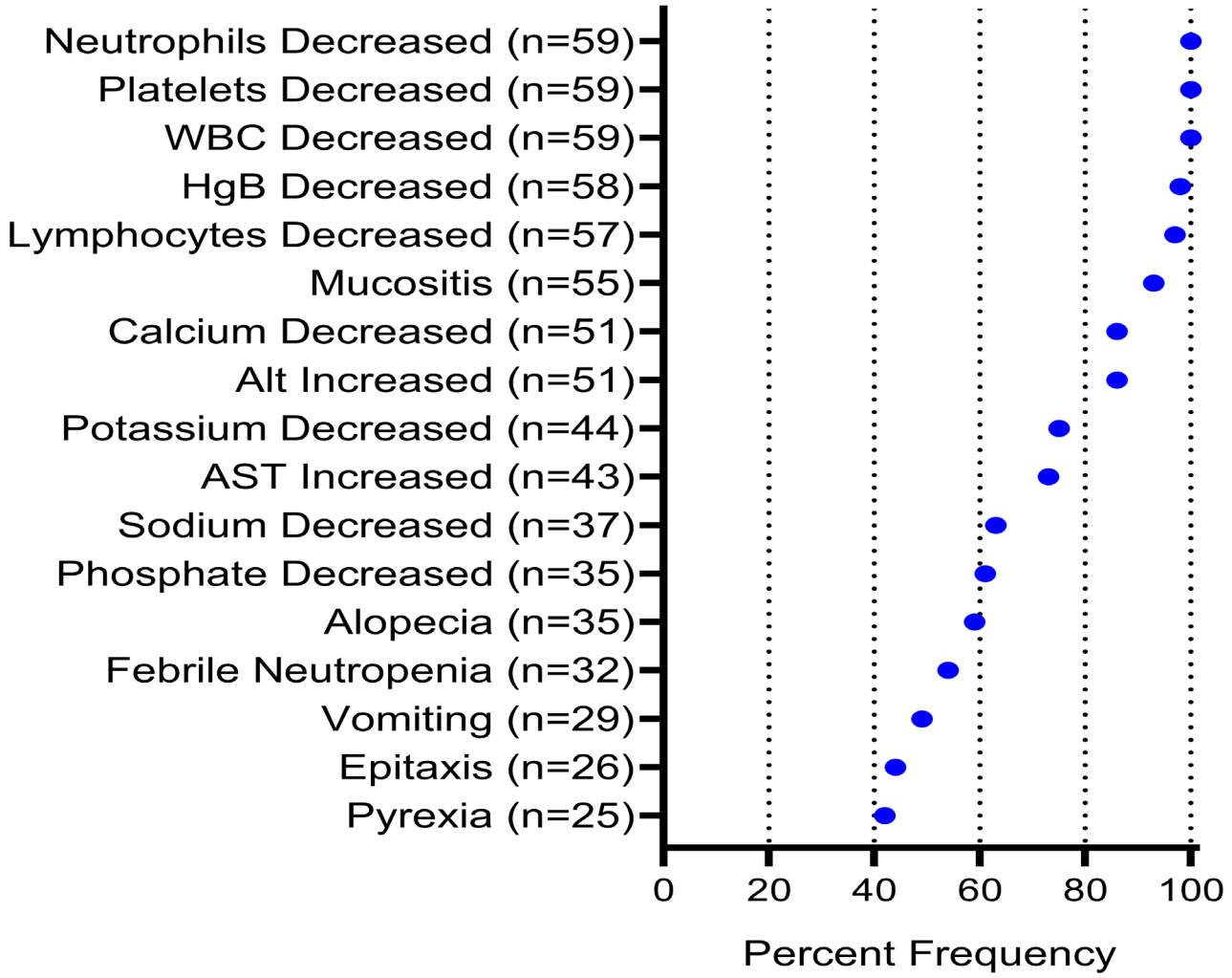
- Subjects followed for median of 2.5 years
  - Range 0.3 - 7

Exposure to Busulfan and Beti-cel

Study	Beti-cel dose	Busulfan dose
HGB-204 N=18	VCN criterion: 0.5-3 c/dg Actual 0.7 (0.3, 1.5) ≥ 3 × 10^6 CD34+ cells/kg Actual 8.1 (5.2, 18.1)	Target dose (µM*min) 3600 to 5000 Actual 4092 (2020, 4714)
HGB-207 N=23	VCN criterion: 0.8-6.6 c/dg Actual 3.3 (1.9, 5.6) ≥ 5 × 10^6 CD34+ cells/kg Actual 8.1 (5, 19.9)	Target dose (µM*min) 3800 to 4500 Actual 4337 (3708, 8947)
HGB-212 N=18	VCN criterion: 0.8-6.6 c/dg Actual 3 (1.2, 7) ≥ 5 × 10^6 CD34+ cells/kg Actual 10.7 (5.9, 42.1)	Target dose (µM*min) 3800 to 4500 Actual 4237 (3605,9086)

Source: Reviewer calculations from ADSL dataset

AEs in ≥ 40% Subjects from Day 1 to Month 24



Source: Reviewer calculations from ISS ADAE and ADLB datasets

Serious Adverse Events (SAEs)

Serious treatment-emergent AEs Reported in ≥ 3 subjects	N=59 n (%) All Grades	N=59 n (%) ≥ Grade 3
Veno occlusive liver disease	5 (8)	5 (8)
Pyrexia	4 (7)	0
Neutropenia	3 (5)	3 (5)
Thrombocytopenia	3 (5)	3 (5)
Thrombosis	3 (5)	2 (3)

Source: Reviewer calculations from ISS ADAE dataset

FDA Safety Concerns

- New or worsening hematologic abnormalities:
  - Delayed platelet engraftment/prolonged thrombocytopenia
- Bone marrow morphology abnormalities
- Lentiviral vector related oligoclonality post beti-cel
- Insertional oncogenesis after treatment with closely related lentiviral vector products

Neutrophil Engraftment Delay

- Neutrophil engraftment (NE):
  - 3 consecutive neutrophil counts ≥ 0.5 x 10^9/L on 3 different days within 42 days of beti-cel infusion

- Applicant reported NE attained by median Day 23 (range 13-39), but:
  - 52% received granulocyte-colony stimulating factor (G-CSF) after beti-cel
  - 17% continued G-CSF ≥ 7 days beyond time of NE
  - 2 subjects (3%) continued G-CSF beyond Day 42

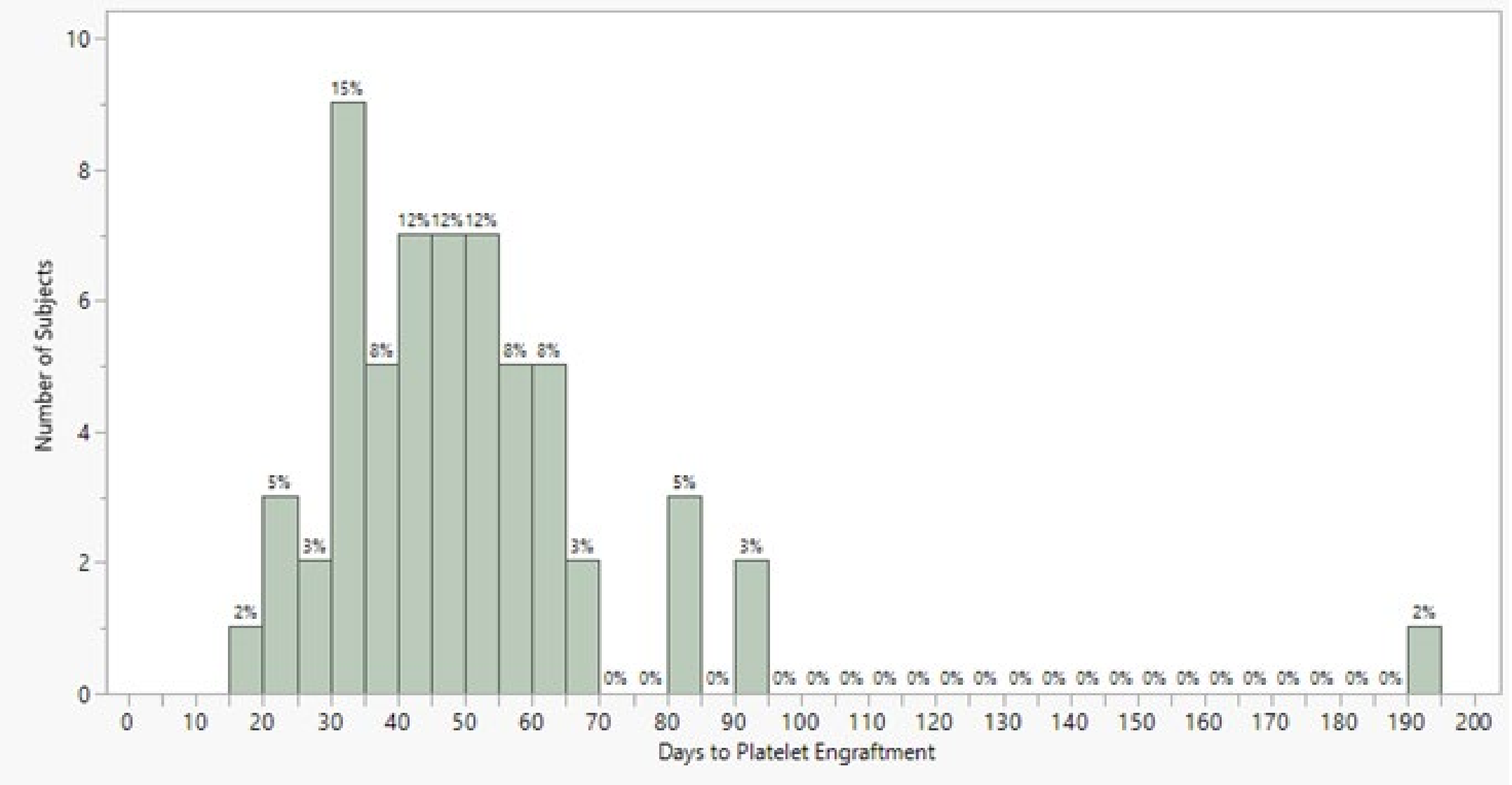
- Adjudicating NE only after each subject discontinued G-CSF gives a median Day 25 to NE (range 13–77)

- Raises question of NE failure in 2 subjects who discontinued G-CSF after Day 42

Delayed Platelet Engraftment

- Platelet engraftment (PE)
  - 3 consecutive platelet values ≥ 20 × 10^9/L on different days, after post-transplant value of < 20 × 10^9/L
  - No platelet transfusions administered for 7 days preceding and during the evaluation period
- Beti-cel associated with delayed platelet engraftment
  - Median time to PE 46 days, range 19-191 days

Platelet Engraftment



Source: Reviewer calculations from PDISE ADSL dataset

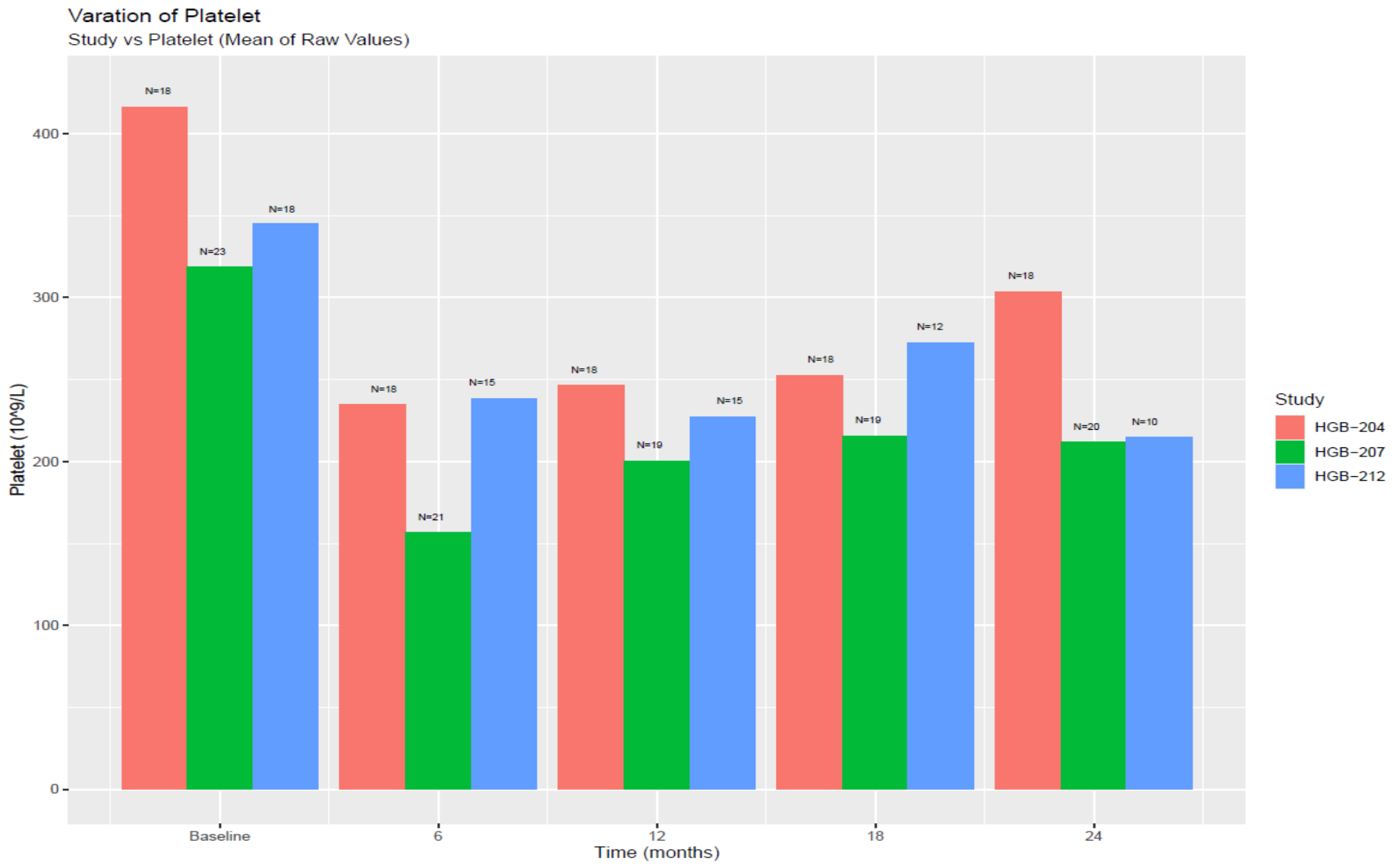
Latent Platelet Reconstitution

- Further platelet reconstitution above 20x10^9/L threshold to reach platelet engraftment was also delayed

- Beti-cel-treated subjects (N=59) reached the first of 3 consecutive unsupported platelet counts of ≥ 100 × 10^9/L at median Day 86 (range 24 - 891)

- 10/59 subjects (17%) continued to experience ≥ grade 3 thrombocytopenia beyond Day 80

Mean Platelet Count: Baseline & Post-beti-cel



Source: FDA Statistician calculations from ISS ADLB dataset

Bone Marrow Morphology Abnormalities

HGB-207

- 4 subjects had post-beti-cel ring sideroblasts but lacked baseline iron stains, making it challenging to ascribe the finding to TDT or study treatment
- 1 subject had emergent monolobated megakaryocytes at Month 12 with borderline thrombocytopenia (158 x10^9/L platelets), of concern for MDS, but declined subsequent Bx

HGB-212

- 20-30% of HGB 212 subjects had persistent ring sideroblasts & dysmegakaryopoietic changes which may obscure determination of emergent marrow pathology

Insertional Oncogenesis Screening

- LVV associated with a risk of insertional oncogenesis
- All subjects receiving beti-cel treatment screened with integration site analysis (ISA) of peripheral blood
- Additional analyses to assess for clones meeting criteria for clonal predominance included:
  - Quantitative polymerase chain (qPCR) reaction
  - Specific integration site primers
- Clonal Predominance:
  - Integration site with a relative frequency of ≥50% and total vector copy number (VCN) of ≥ 0.1 copies per diploid genome
- Oligoclonality (proposed definition):
  - Integration site with relative frequency of ≥10% and VCN of ≥ 0.1 copies per diploid genome

Insertional Oncogenesis Concerns

- Malignancy and clonal predominance has not been reported post beti-cel
- 3 subjects with TDT met the integration site oligoclonality definition
- 2 of these had persistent, stable oligoclonality
  - 1st subject did not reach platelets of ≥ 100x10^9/L as of Day 737; and had expansion of a clone containing at least two integration sites, into proto-oncogenes, *XP07* and *CBFB*
  - 2nd subject did not reach platelet ≥ 100x10^9/L until after Day 501; but showed a pattern of integration sites that is consistent with a clone containing multiple integration sites, or expansion of several clones to a similar extent. One of these integration sites being at proto-oncogene *BCR*
  - 3rd subject has oligoclonality in *MAP4K2* with single IS of ≥ 10% RelFreq, but with normal platelet reconstitution
- In 2 subjects, the location of integrations into proto-oncogenes is of concern

LVV Integrations into Genes of Concern

- 56% of subjects with TDT had LVV integrations into *VAMP4* gene
  - With 59 unique *VAMP4* integration sites detected (highest max freq. 0.2%)

- No correlation noted between *VAMP4* gene LVV integration and delayed platelet reconstitution

- *VAMP4* gene LVV integrations also reported in leukemic cells in 1 subject with sickle cell disease (SCD) after lovo-cel infusion
  - Lovo-cel: LVV product for SCD; manufactured using LVV identical to beti-cel

LVV Integration after Lovo-cel for SCD

- Acute myeloid leukemia (AML) reported in 2 of 49 subjects with SCD treated with lovo-cel

- One subject with AML had blasts containing prominent LVV integration into VAMP4 gene
  - Causality of VAMP4 LVV integration in the AML unproven

Tentative MDS Cases Post Lovo-cel

- One subject developed anemia after lovo-cel treatment for SCD
- MDS was diagnosed after scheduled 6-month bone marrow biopsy showed hypoplasia of myeloid precursors & cytogenetic aberrancy (trisomy 8 & tetrasomy 8) on fluorescent in situ hybridization (FISH)
- Later, MDS diagnosis changed to transfusion-dependent anemia, after repeat marrow tests were felt to reflect “stress erythropoiesis", and repeat FISH test for trisomy 8 negative
- Another subject with SCD and anemia: marrow testing 12 months post lovo-cel found erythroid dysplasia, persistent trisomy 8 & tetrasomy 8 (by FISH)
  - Concurrent vitamin B12 deficiency

Cerebral Adrenoleukodystrophy (CALD)

- Eli-cel: product manufactured with related LVV for treatment of CALD; given to 67 subjects
  - 2 Two eli-cel recipients developed myelodysplastic syndrome (MDS) with predominant clone containing LVV integration into proto-oncogene (MECOM) & EVI1 overexpression
  - 3rd eli-cel recipient has MDS due to LVV integration into paralog of MECOM, PRDM16
- Additional cases concerning for evolving insertional oncogenesis after eli-cel have
  - Integration sites with increasing relative frequency into proto-oncogenes
  - All had MECOM integrations and IS into other proto-oncogenes
  - One of these subjects prolonged thrombocytopenia and required eltrombopag
- These cases are worrisome for evolution to MDS

Beti-cel Safety Summary

- Safety profile largely as expected with autologous HSCT
- Frequent delay of platelet engraftment & incomplete platelet recovery
- Potentially emergent marrow abnormalities
- No clonal predominance nor insertional oncogenesis reported in beti-cel studies
- After related LVV product lovo-cel,
  - 1 subject with SCD developed AML with LVV integration into VAMP4 in blasts;
  - 2 developed cytogenetic aberrancy (trisomy 8); one becoming transfusion-dependent
- 3 subjects treated with product manufactured with related LVV for CALD developed MDS with integration into a proto-oncogene; other subjects with cytopenias and/or clonal expansion

Safety Conclusion

- Role of LVV integrations in etiology of delayed platelet engraftment among beti-cel recipients is uncertain

- Hematologic malignancies observed after treatment with LVV-based products for SCD and CALD increase FDA's concern that abnormal platelet reconstitution may progress to MDS

Benefit-Risk Assessment

Benefit

- Clinical studies demonstrate that 89% of subjects with TDT given beti-cel treatment achieve primary efficacy endpoint of transfusion - independence

- Durability of transfusion - independence demonstrated through approximately 39 months follow-up in Phase 3 studies

Risk

- Prevalent delay in platelet engraftment and prolonged thrombocytopenia

- Concerns regarding insertional oncogenesis, given:
  - AML and MDS reported with the Applicant's LVV products for SCD and CALD
  - Bone marrow morphologic abnormalities in beti-cel recipients
  - Oligoclonality in some beti-cel recipients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