Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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beti-cel & eli-cel Advisory Committee Meeting Introduction – June 10, 2022

betibeglogene autotemcel (beti-cel)

Anne-Virginie Eggimann, MSc

Chief Regulatory Officer

bluebird bio, Inc.

bluebirdbio®

Proposed Indication

beti-cel is for the treatment of

patients with β-thalassemia who require regular red blood cell transfusions

β-thalassemia is a Life-shortening Disease

- **A rare genetic blood disease caused by mutations in the β-globin gene (*HBB*)**
- **Results in anemia due to reduced or absent production of functional adult hemoglobin (HbA)**
- **For severe anemia, lifelong regular red blood cell (RBC) transfusions are required for survival**
- **Regular transfusions lead to inevitable accumulation of iron causing end-organ damage, and shortened lifespan**

Taher et al., *N Engl J Med.* 2021; 384:727-743.
Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021.

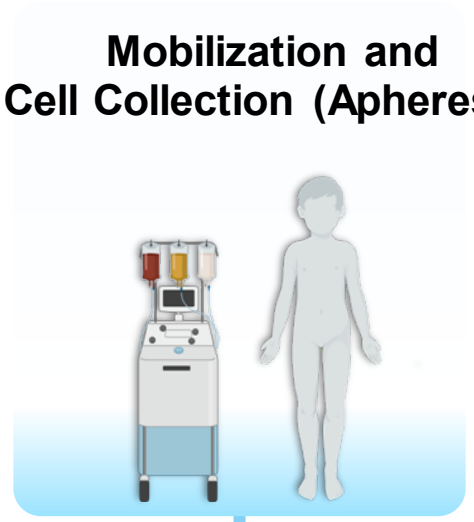
betibeglogene autotemcel (beti-cel)

- First-in-class, one-time, lentiviral vector (LVV) gene therapy
- Consists of patient's own blood stem cells that have been genetically modified ex vivo with BB305 LVV
- In vivo, these cells differentiate into red blood cells with sufficient functional beti-cel derived HbA to eliminate red blood cell transfusions in most patients

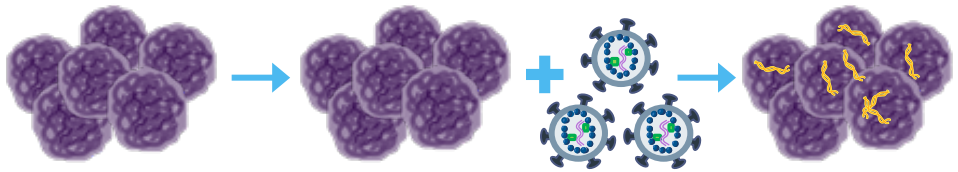
HbA: adult hemoglobin

beti-cel Produces Functional Adult Hemoglobin Referred to as HbA^{T87Q}

Mobilization and Cell Collection (Apheresis)



Manufacturing



Select CD34+ cells

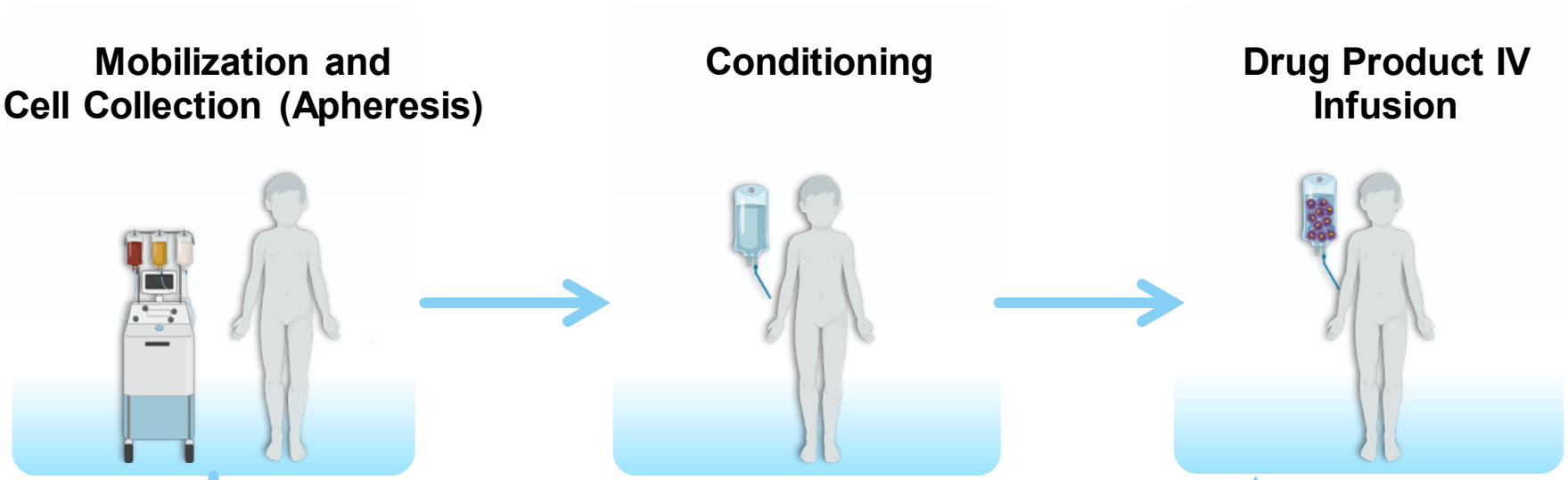
Transduce Cells with Lentiviral Vector (LVV)

Cryopreserve, Test, and Release Drug Product

BB305 LVV adds $\beta^{A\text{-}T87Q}$-globin gene

HbA^{T87Q}: hemoglobin containing $\beta^{A\text{-}T87Q}$-globin

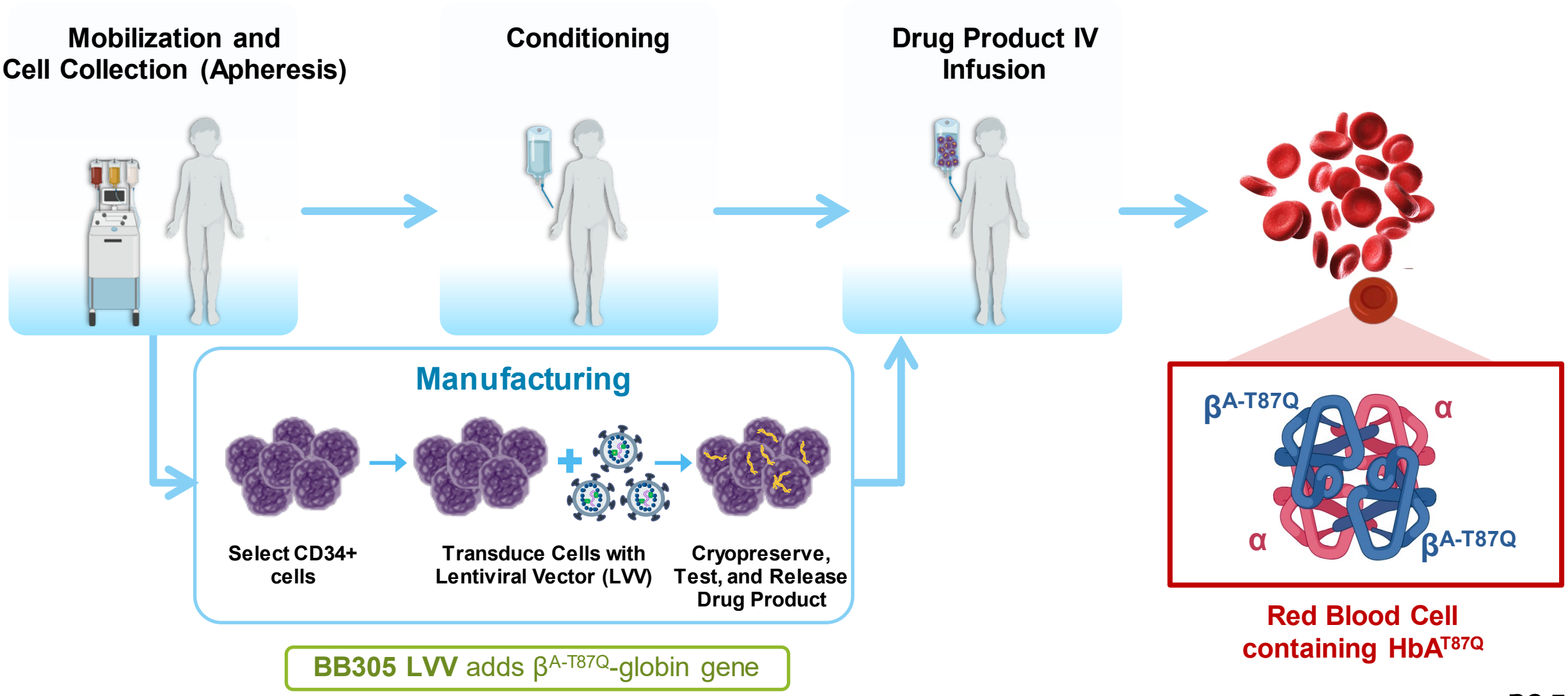
beti-cel Produces Functional Adult Hemoglobin Referred to as HbA^{T87Q}



BB305 LVV adds $\beta^{A\text{-}T87Q}$-globin gene

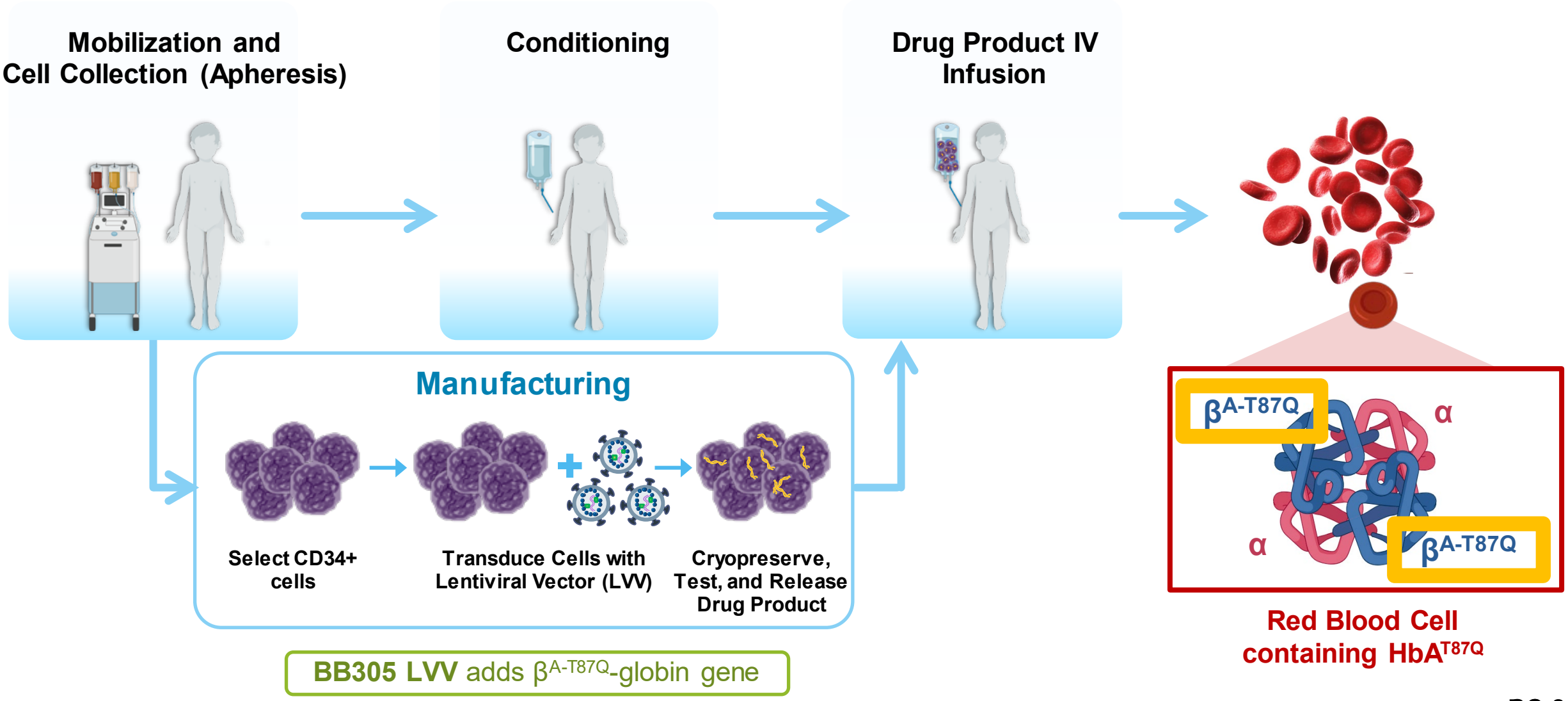
HbA^{T87Q}: hemoglobin containing $\beta^{A\text{-}T87Q}$-globin; IV: intravenous

beti-cel Produces Functional Adult Hemoglobin Referred to as HbA^{T87Q}



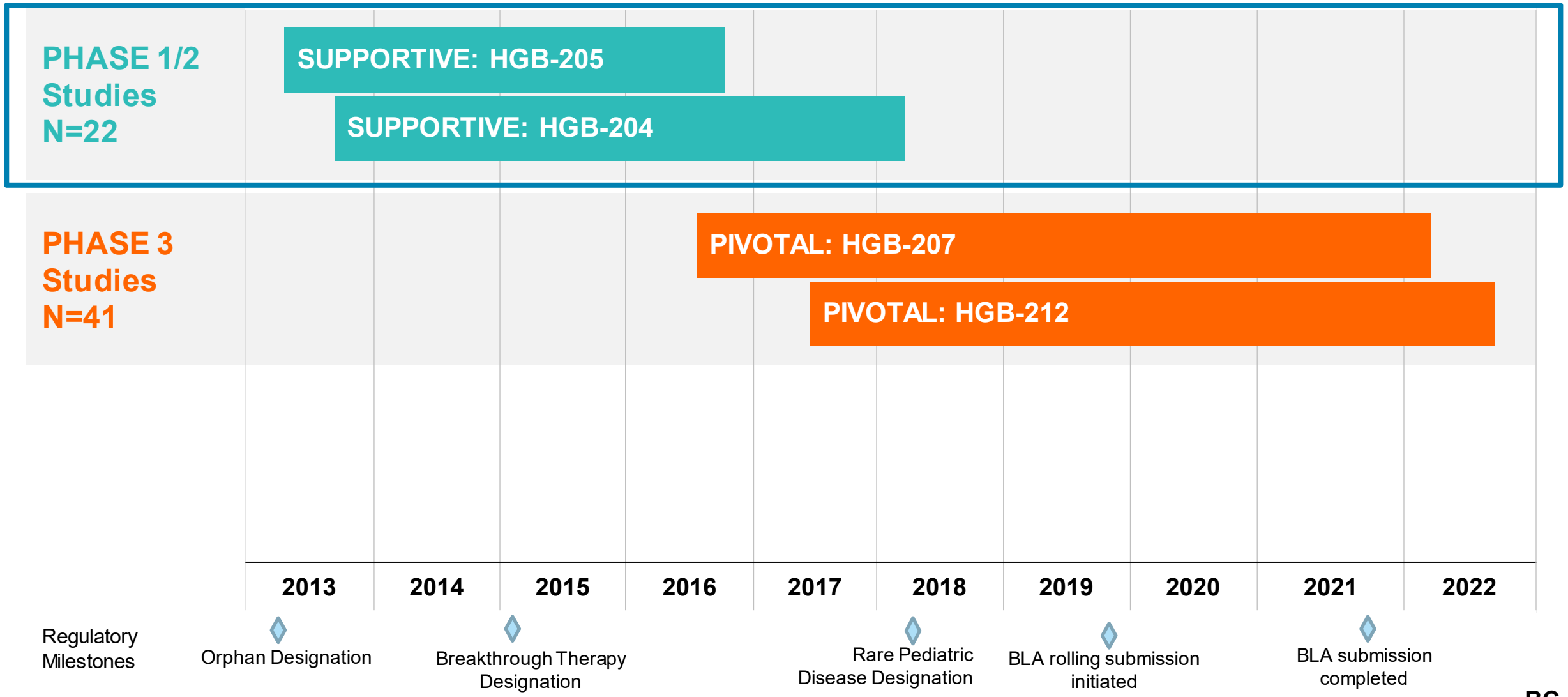
HbA^{T87Q}: hemoglobin containing $\beta^{A\text{-}T87Q}$-globin; IV: intravenous

beti-cel Produces Functional Adult Hemoglobin Referred to as HbA^{T87Q}

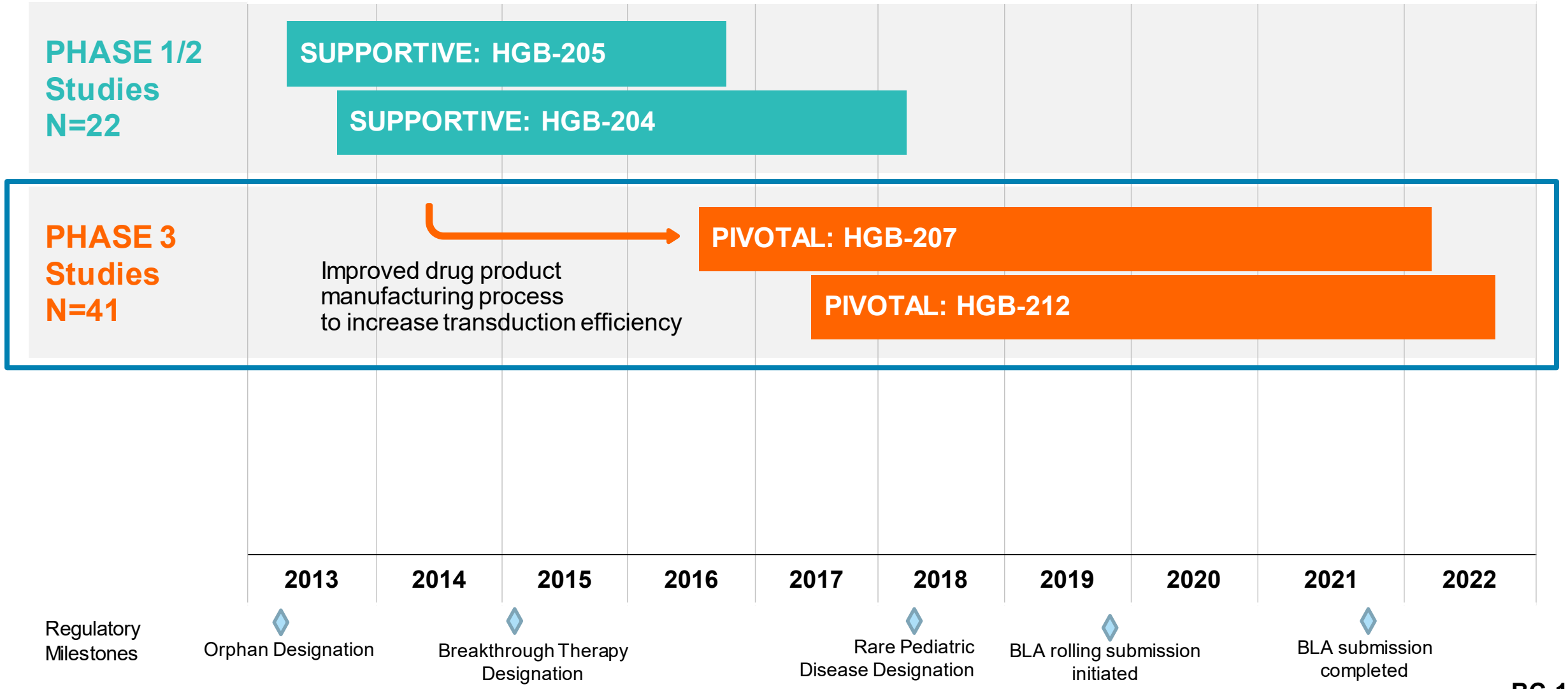


HbA^{T87Q}: hemoglobin containing β^{A-T87Q}-globin; IV: intravenous

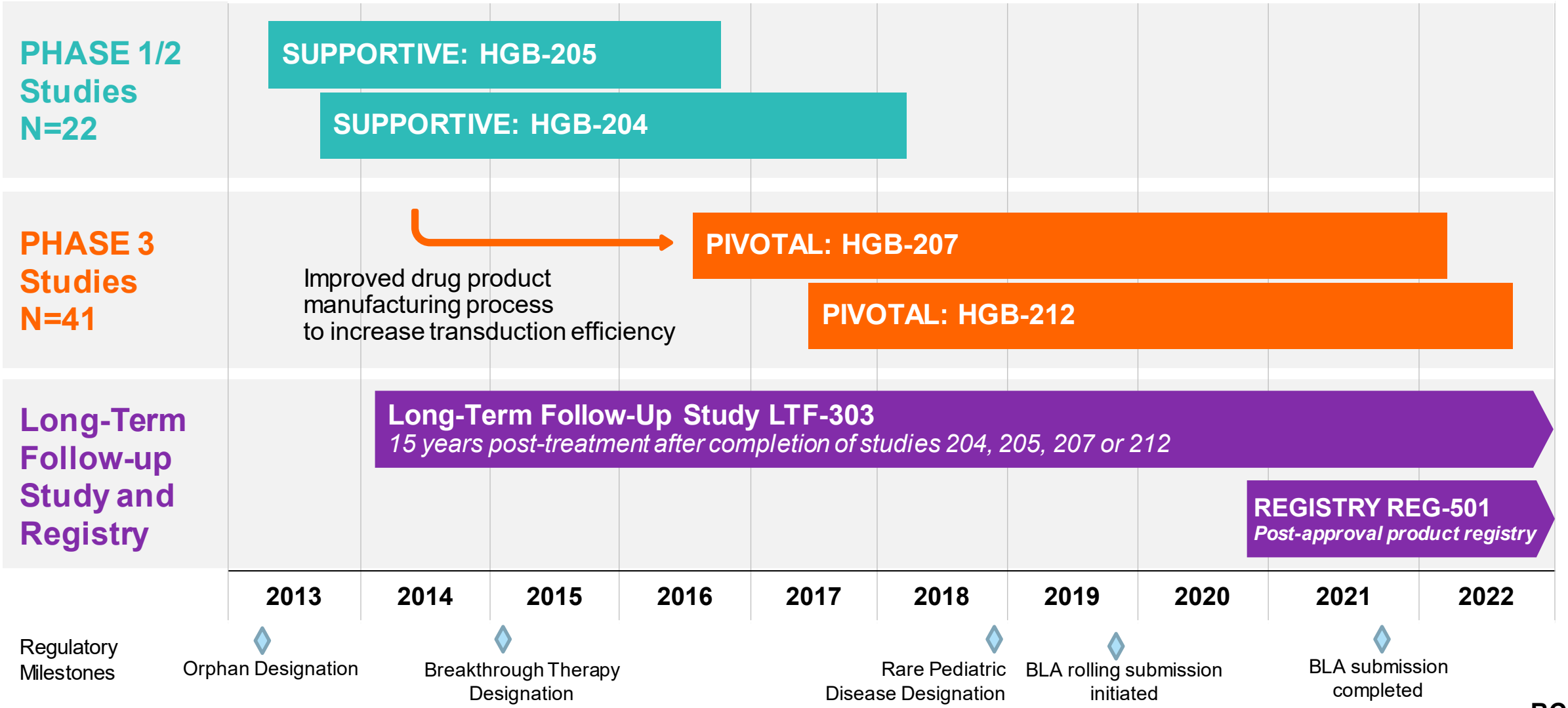
Overview of beti-cel Clinical Development



Overview of beti-cel Clinical Development



Overview of beti-cel Clinical Development



beti-cel Positive Benefit/Risk Profile

- **High rate of durable transfusion independence**

Data-cut date: March 10, 2021

beti-cel Positive Benefit/Risk Profile

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- Trends of improvement in iron overload and erythropoiesis

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- Safety profile largely reflects known side effects of mobilization and conditioning agents

Data-cut date: March 10, 2021

beti-cel Positive Benefit/Risk Profile

- High rate of durable transfusion independence
- Trends of improvement in iron overload and erythropoiesis
- Safety profile largely reflects known side effects of mobilization and conditioning agents
- No BB305 LVV mediated safety event, no malignancy, no death

Data-cut date: March 10, 2021
LVV: lentiviral vector

Agenda for Sponsor Presentations – June 10, 2022

Introduction	**Anne-Virginie Eggimann, MSc** Chief Regulatory Officer, bluebird bio, Inc.
Unmet Medical Need	**Sujit Sheth, MD** Chief, Pediatric Hematology/Oncology & Professor of Clinical Pediatrics at Weill Cornell Medical Center
Efficacy	**Rich Colvin, MD, PhD** Chief Medical Officer, bluebird bio, Inc.
Safety	**Ajay Singh, MD** Vice President Pharmacovigilance, bluebird bio, Inc.
Benefit-Risk	**Alexis Thompson, MD, MPH** Chief, Hematology Children's Hospital of Philadelphia

Additional Experts – June 10, 2022

Bone Marrow Assessments	**Shunyou Gong, MD, PhD** Director of Hematology and Hematopathology Ann & Robert H. Lurie Children's Hospital of Chicago Associate Professor of Pathology Northwestern University Feinberg School of Medicine
	Robert Hasserjian, MD Professor of Pathology Harvard Medical School
Hematologic Oncology	**R. Coleman Lindsley, MD, PhD** Assistant Professor, Medical Oncology Dana-Farber Cancer Institute
Pediatric Hematopoietic Stem Cell Transplantation	**Timothy S. Olson, MD, PhD** Medical Director, Blood and Marrow Transplant Program Children's Hospital of Philadelphia
Gene Therapy	**David A. Williams, MD** Chief of Hematology/Oncology at Boston Children's Hospital Senior Vice President, Chief Scientific Officer at Boston Children's Hospital Professor of Pediatrics at Harvard Medical School

Unmet Need in Patients with β-Thalassemia who Require Regular Red Blood Cell Transfusions

Sujit Sheth, M.D.

Chief, Pediatric Hematology/Oncology &

Professor of Clinical Pediatrics at Weill Cornell Medical Center

β-Thalassemia is an Inherited, Life-long Condition

High burden of disease and complications

Early initiation of regular transfusions, chelation, monitoring

Very cumbersome, hospital time-intense, expensive treatment

Negative impact on survival and quality of life

Huge unmet need for curative options

Genotypic Classification

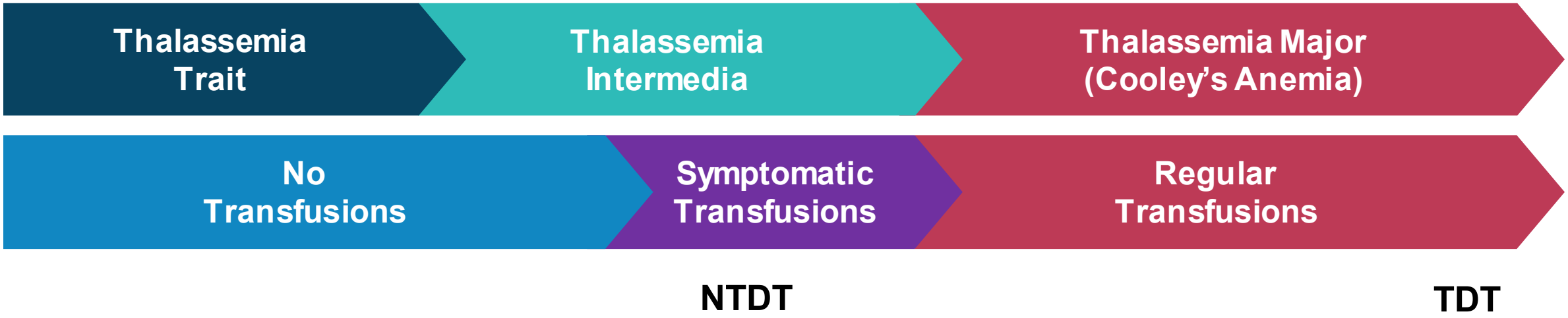
- **Nearly 350 mutations have been identified that may cause β-thalassemia[1]**
- **Mutations may be**

β^0	No functional β-globin production[1,2]
β^+	Reduced functional β-globin production[1,2]
β^E	Reduced functional β-globin production (primarily found in Southeast Asia)[1,2]

- **Broadly classified as β^0/β^0 or non-β^0/β^0**

1. Taher et al., *N Engl J Med.* 2021; 384:727-743.
2. Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021.

Phenotypes - Clinical Spectrum of Disease



Both β^0/β^0 and non-β^0/β^0 genotypes may be transfusion-dependent

NTDT: non-transfusion-dependent β-thalassemia; TDT: transfusion-dependent β-thalassemia.

Taher et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (NTDT).* Thalassaemia International Federation, 2013.
Karimi et al., *Pediatr Hematol Oncol.* 2014; 31(7):583-596.
Musallam et al., *Haematologica.* 2011; 96(11):1605-1612
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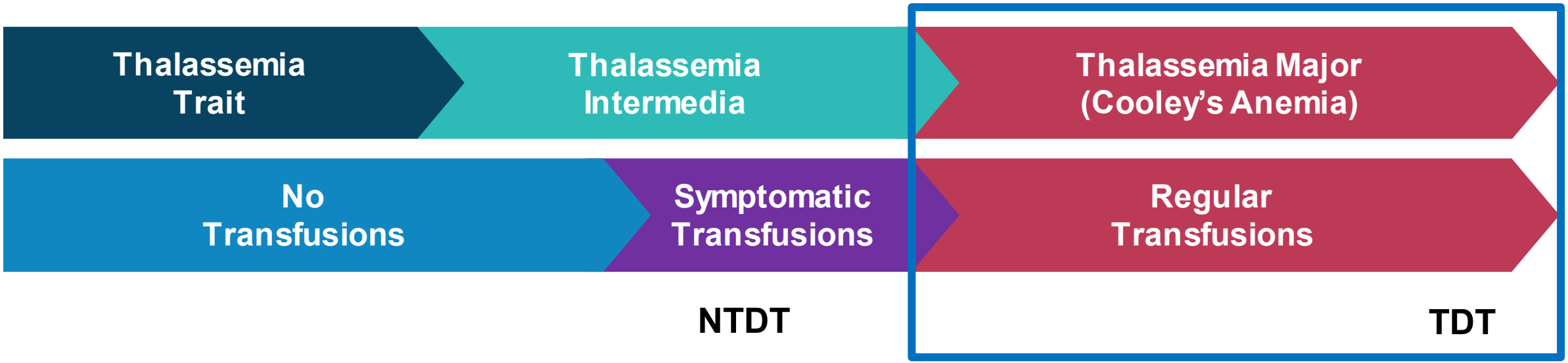

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Current Treatment Options are Limited

Chronic Therapy

All TDT Patients

Blood transfusions and iron chelation therapy[1,2]

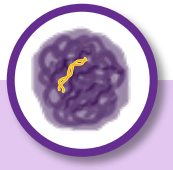
- Standard of care
- Transfusions required every 2-5 weeks
- Monitoring for disease and treatment-related complications

TDT Patients ≥18 Years

luspatercept[1,3]

- Addition to standard of care
- Dosing every 3 weeks subcutaneously by HCP
- Goal - reduce transfusion requirement

Potentially Curative Therapy



Allogeneic HSCT [1,2]

- Primarily offered to children and young adolescents with TDT
- Option available to ~25% with matched sibling donor
  - Overall thalassemia free survival is ~ 90%[4]
- Best results when done early before
  - Alloimmunization
  - Iron related organ damage

TDT: transfusion-dependent β-thalassemia; HCP: healthcare provider; HSCT: hematopoietic stem cell transplant.

1. Taher A, et al. *N Engl J Med*. 2021;25;384(8):727-743. 2. Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021.3. Reblozyl (luspatercept) [prescribing information]. Princeton, NJ: Bristol Myers Squibb; October 2021. 4. Li C, et al., *Blood Adv.* 2019;3(17):2562-2570.

Allo-HSCT is a Potentially Curative Option for Limited Patient Population

Marked Improvement Post-Transplant

No more transfusions, chelation discontinued once iron levels "normalized"

Marked improvement in quality of life

Potential risks: Mortality, GvHD, graft failure, graft rejection – higher risk with mismatched donor

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Accepted as part of the treatment paradigm

Limited accessibility based on donor availability in only 25% of patients

Underscores need for curative therapy available to all

Allo-HSCT: allogeneic hematopoietic stem cell transplant; GvHD: graft versus host disease.

Angelucci et al. *Haematologica* 2014, 99 (5):811-820.

Typical Journey of a Patient with TDT

Initiate regular monthly RBC transfusions at young age

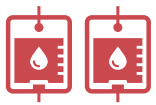
Start iron chelation

Annual liver MRI from age 2 yrs and chelator associated monitoring

FIRST DECADE

Increased transfusion - 2-3 units every 2-5 weeks

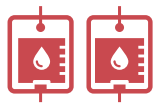
Continue chelation – reinforce compliance



Annual liver and cardiac MRI after age 10 years
Chelator associated monitoring

SECOND DECADE

Ongoing regular transfusions & chelation



Annual MRI: Liver, Cardiac
Chelator associated monitoring
Bone density
Endocrine assessments

ADULTHOOD

Iron Overload Complications

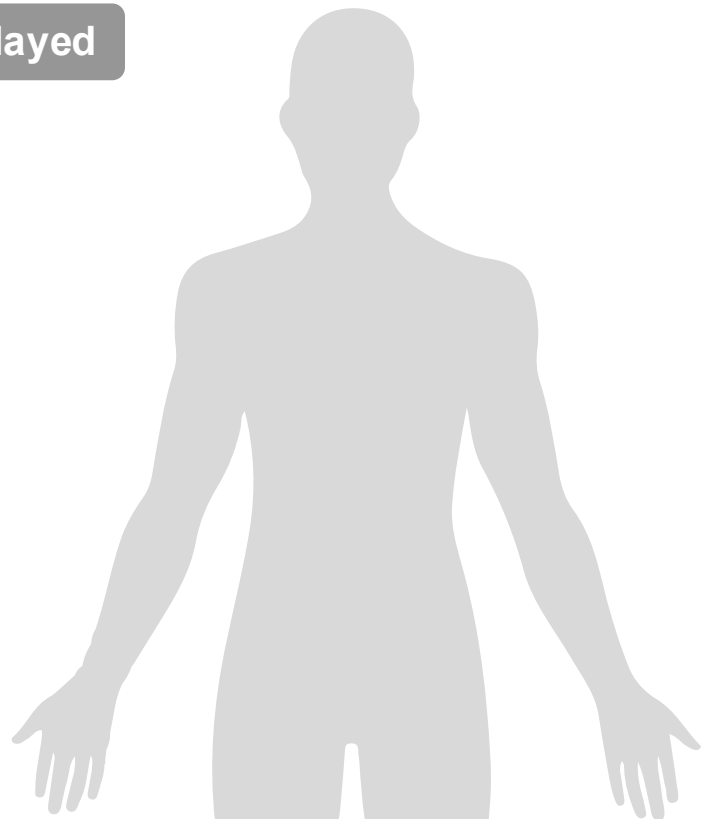
Delayed Growth	Delayed puberty Diabetes Other endocrinopathies Heart failure	Secondary amenorrhea Infertility Osteoporosis and fractures Liver disease

TDT: transfusion-dependent β-thalassemia; RBC: red blood cells; MRI: Magnetic Resonance Imaging.

β-Thalassemia is Characterized by Ineffective Erythropoiesis and Hemolysis that can Lead to Several Clinical Complications [1-3]

Disease-related, if NTDT or transfusion delayed

- **Ongoing ineffective erythropoiesis**
  - **Chronic anemia**
  - **Extramedullary hematopoiesis**
  - **Bone deformity, osteopenia**
- **Impaired growth & development**
- **Vascular disease**
  - **Cerebral infarcts**
  - **Pulmonary hypertension**
- **Iron overload**



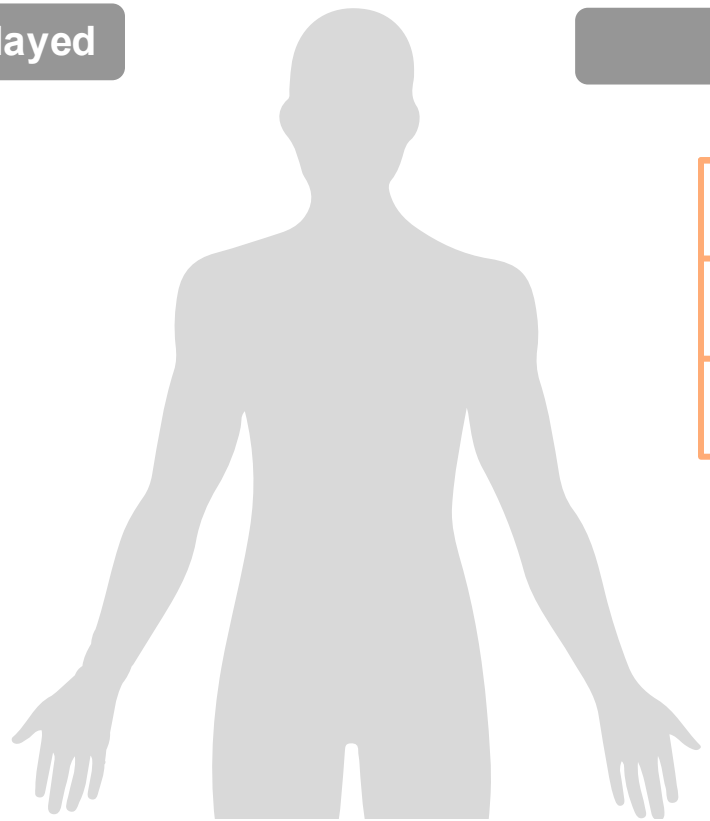
QoL / Mental health issues

[a]There have been significant decreases in in transfusion-transmitted infections owing to improvement in blood screening.[4,5]

NTDT: non-transfusion-dependent β-thalassemia; QoL: Quality of Life.

1. Galanello R, et al. *Orphanet J Rare Dis.* 2010;5:11. 2. Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021. 3. Rund D, et al. *N Engl J Med.* 2005;353(11):1135-1146. 4. Schreiber GB, et al. *N Engl J Med.* 1996;334(26):1685-1690. 5. FDA. Fatalities reported to FDA following blood collection and transfusion: annual summary for FY2016. Available at: https://www.fda.gov/media/111226/download. Accessed 25 January 2022.

β-Thalassemia is Characterized by Ineffective Erythropoiesis and Hemolysis that can Lead to Several Clinical Complications [1-3]



Disease-related, if NTDT or transfusion delayed

- Ongoing ineffective erythropoiesis
  - Chronic anemia
  - Extramedullary hematopoiesis
  - Bone deformity, osteopenia
- Impaired growth & development
- Vascular disease
  - Cerebral infarcts
  - Pulmonary hypertension
- Iron overload

QoL / Mental health issues

Treatment-related

- Transfusion-related
  - Transfusion reactions
  - Bloodborne infections
  - Iron overload
- Endocrinopathies
- Liver fibrosis, cirrhosis, carcinoma
- Cardiomyopathy / arrhythmias
- Chelator toxicity

[a]There have been significant decreases in in transfusion-transmitted infections owing to improvement in blood screening.[4,5]

NTDT: non-transfusion-dependent β-thalassemia; QoL: Quality of Life

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Causes of Mortality

CARDIOVASCULAR COMPLICATIONS

As a result of iron overload remain a leading cause of death[1,2]

OTHER CAUSES OF DEATH

Include liver disease, infections, and vascular events[1,2]

2022 analysis from Cooley's Anemia Foundation (CAF) database[3] :

- 792 patients with TDT
- 50 deaths reported between 2011 and 2021
- **Median age of death was 37 years (range: 6 mo – 58 yrs)**

TDT: transfusion-dependent β-thalassemia.

1. Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021. 2. Betts et al., *Clin Ther* 2020; 42(2) 322-337. 3. Cooley's anemia foundation: https://www.thalassemia.org/2021-caf-information/

Patients Require Comprehensive Life-long Monitoring for Disease and Treatment-Related Complications

Every 3 Months

- Serum ferritin
- Liver and kidney function
- Height and weight (pediatrics)

Every 6 Months

- Vitamin D
- Growth velocity and Tanner Stage (pediatrics)
- RBC transfusion volume

Every 12 Months

- Liver MRI, ultrasound
- Cardiac T2* (MRI), ECG, echocardiogram
- Hepatitis A, B, C serology
- Audiology evaluation
- Ophthalmology evaluation
- Examination in adults:
  - T3, fT4, TSH, PTH Testosterone/ Estrogen
  - Oral Glucose tolerance

Every 24 Months

- Bone mineral densitometry
- Fibroscan

Regular assessment of quality of life

ECG, electrocardiogram; fT4, free T4 hormone; Hb, hemoglobin; LFT, liver function test; MRI, magnetic response imaging; PTH, parathyroid hormone; RBC, red blood cell; T2*, magnetic resonance imaging of cardiac T2; T3, triiodothyronine; TDT, transfusion-dependent β-thalassemia; TSH, thyroid-stimulating hormone.

1. Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021. 2. Vichinsky E, et al. *Standards of Care Guidelines for Thalassemia.* Oakland, CA: Children's Hospital & Research Center Oakland; 2012. 3. Cooley's Anemia Foundation. Guidelines for Managing Transfusion Therapy for Thalassemia. https://www.thalassemia.org/boduw/wp-content/uploads/2018/05/Guidelines-for-Managing-Transfusion-Therapy-for-Thalassemia.pdf. Accessed November 9, 2021.

Patients Experience Life-Long High Treatment-Related Burden

Patients are tethered life-long to the healthcare system

Yearly Burden of 48 Blood Bags for a Patient Receiving 2 RBC Units Every 2 Weeks

15-25 RBC transfusion episodes/year[1-3]

Requires 9+ hours of TDT management on transfusion days[4], longer if alloantibodies or have reactions

Anxiety, Pain & Fatigue experienced leading up to each transfusion day[4]

High healthcare resource utilization and impaired work productivity[5,6]

RBC: red blood cells; TDT: transfusion-dependent β-thalassemia.

1. Capellini et al., *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT),* Thalassaemia International Federation, 4th ed. 2021. 2. Taher et al. *N Engl J Med* 2021; 384:727-743. 3. Cooley's Anemia Foundation, Thalassemia Management Checklists. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2018/05/Guidelines-for-Managing-Transfusion-Therapy-for-Thalassemia.pdf. Accessed November 9, 2021. 4. Paramore et al., 2021 *Patient* 14(2):197-208. 5. Weiss et al. 2019 *Am J Hematol*; 94(5):E129-E132. 6. Shah et al., 2021 *eJHaem*; 2(4):738-749.

There is a Significant Need for a More Widely Available Curative Treatment Option

Regular transfusion and more effective iron chelation have played a central role in extending life expectancy for patients with β-thalassemia[1,2]

Allogeneic HSCT is a potentially curative option in limited number of patients[3,4]

However, these treatments and their potential complications continue to have a significant impact on lives of patients and their families

HSCT: hematopoietic stem cell transplant.

1. Borgna-Pignatti C et al. *Haematologica*. 2004;89:1187-1193. 2. Tubman et al., *J Pediatr Hematol Oncol.* 2015; 37:e162-e169. 3. Li C, et al., *Blood Adv.* 2019;3(17):2562-2570. 4. Baronciani et al., *Bone Marrow Transplant.* 2016:51(4):536-541.

Efficacy

Richard Colvin, MD, PhD

Chief Medical Officer

bluebird bio, Inc.

Overview of Clinical Development of beti-cel

Overview of Clinical Development of beti-cel

HGB-205 Completed

- Non-β^0/β^0
- N=4: ≥12 years

HGB-204 Completed

- Non-β^0/β^0 and β^0/β^0
- N=18: 15 patients ≥18 years
  3 patients ≥12 and <18 years

Overview of Clinical Development of beti-cel

HGB-205 Completed

- Non-β^0/β^0
- N=4: ≥12 years

HGB-204 Completed

- Non-β^0/β^0 and β^0/β^0
- N=18: 15 patients ≥18 years
  3 patients ≥12 and <18 years

HGB-207 Ongoing

- Non-β^0/β^0
- Cohort 1: N=15: ≥12 years
- Cohort 2: N=8: <12 years

HGB-212 Ongoing

- β^0/β^0, $\beta^{+IVS\text{-}1\text{-}110}/\beta^{+IVS\text{-}1\text{-}110}$, and $\beta^0/\beta^{+IVS\text{-}1\text{-}110}$
- N=18: 5 patients ≥18 years
  13 patients <18 years

Overview of Clinical Development of beti-cel

HGB-205 Completed

- Non-β^0/β^0
- N=4: ≥12 years

HGB-204 Completed

- Non-β^0/β^0 and β^0/β^0
- N=18: 15 patients ≥18 years
  3 patients ≥12 and <18 years

HGB-207 Ongoing

- Non-β^0/β^0
- Cohort 1: N=15: ≥12 years
- Cohort 2: N=8: <12 years

HGB-212 Ongoing

- β^0/β^0, $\beta^{+IVS\text{-}1\text{-}110}/\beta^{+IVS\text{-}1\text{-}110}$, and $\beta^0/\beta^{+IVS\text{-}1\text{-}110}$
- N=18: 5 patients ≥18 years
  13 patients <18 years

LTF-303 Ongoing

- Total of 15 years post beti-cel treatment
- N=51

Key Characteristics of Phase 3 Studies

Key Eligibility Criteria

Transfusion-dependent β-thalassemia

- ≥100 mL/kg/year of packed red blood cells (pRBC)
  OR
  ≥8 pRBC transfusions/year

GENOTYPES

- HGB-212: β^0/β^0, $\beta^{+IVS\text{-}1\text{-}110}/\beta^{+IVS\text{-}1\text{-}110}$, $\beta^0/\beta^{+IVS\text{-}1\text{-}110}$
- HGB-207: non-β^0/β^0

AGE

- ≤50 years

TDT, transfusion-dependent β-thalassemia defined as receiving ≥100 mL/kg/yr packed red blood cell transfusions or ≥8 transfusion episodes per year in the 2 years preceding enrollment.
HGB-207 (NCT02906202), HGB-212 (NCT03207009)

Key Characteristics of Phase 3 Studies

Key Eligibility Criteria

Transfusion-dependent β-thalassemia

- ≥100 mL/kg/year of packed red blood cells (pRBC)
  OR
  ≥8 pRBC transfusions/year

GENOTYPES

- HGB-212: β^0/β^0, $\beta^{+IVS\text{-}1\text{-}110}/\beta^{+IVS\text{-}1\text{-}110}$, $\beta^0/\beta^{+IVS\text{-}1\text{-}110}$
- HGB-207: non-β^0/β^0

AGE

- ≤50 years

Primary Endpoint

Proportion of patients meeting transfusion independence

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

pRBC: packed red blood cells; Hb: hemoglobin
HGB-207 (NCT02906202), HGB-212 (NCT03207009)

HGB-207 and HGB-212: Patient Characteristics at Enrollment

Parameters	HGB-207 N=23		HGB-212 N=18	
Genotype n, (%)	β^{+}/β^{0}	12 (52)†	β^{0}/β^{0}	12 (67)
	β^{E}/β^{0}	6 (26)	$\beta^{+IVS\text{-}1\text{-}110}/\beta^{+IVS\text{-}1\text{-}110}$	3 (17)
	β^{+}/β^{+}	5 (22)‡	$\beta^{0}/\beta^{+IVS\text{-}1\text{-}110}$	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 β+ IVS-1-5 mutation
‡Includes 2 patients who are heterozygous for the β+ IVS-1-110 mutation and 2 patients homozygous for the β+ IVS-1-5 mutation
^Annualized retrospective data for 2 years prior to enrollment

HGB-207 and HGB-212: Patient Characteristics at Enrollment

Parameters	HGB-207 N=23		HGB-212 N=18	
Genotype n, (%)	β^{+}/β^{0}	12 (52)†	β^{0}/β^{0}	12 (67)
	β^{E}/β^{0}	6 (26)	$\beta^{+IVS\text{-}1\text{-}110}/\beta^{+IVS\text{-}1\text{-}110}$	3 (17)
	β^{+}/β^{+}	5 (22)‡	$\beta^{0}/\beta^{+IVS\text{-}1\text{-}110}$	3 (17)
Age at consent, median (min – max), years	15 (4 – 34)		12.5 (4 – 33)	
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Genotype n, (%)	β^+/β^0	12 (52)†	β^0/β^0	12 (67)
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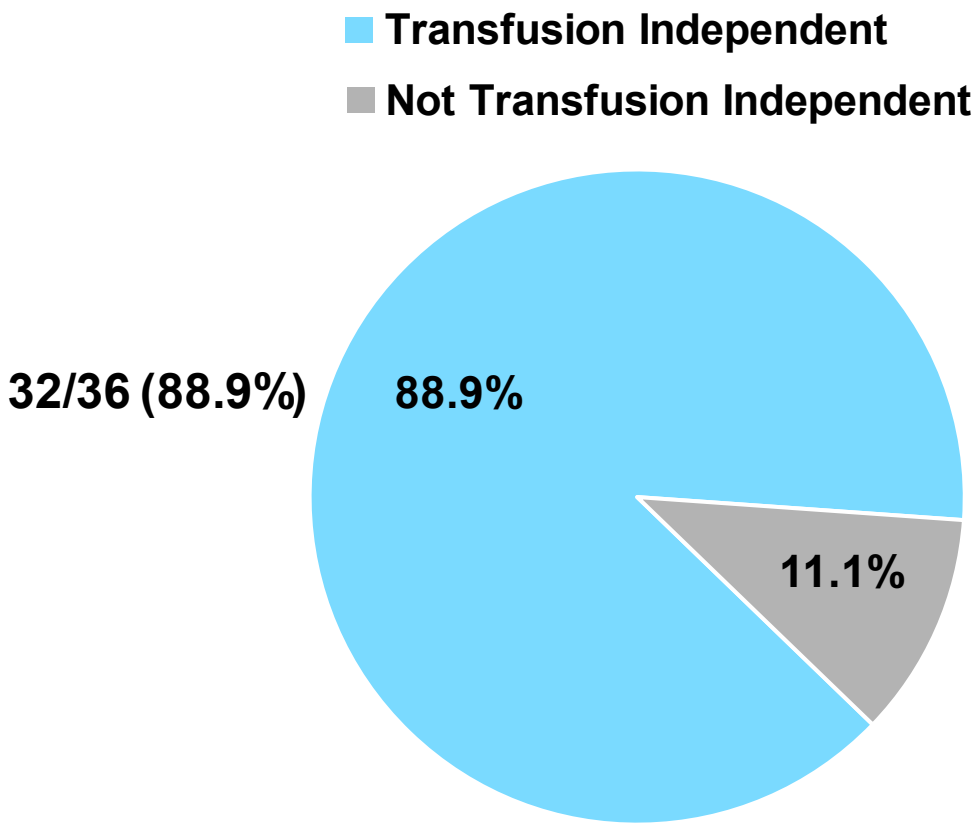
^Annualized retrospective data for 2 years prior to enrollment

32/36 (88.9%) of Evaluable Patients in the Phase 3 Studies Achieved Transfusion Independence

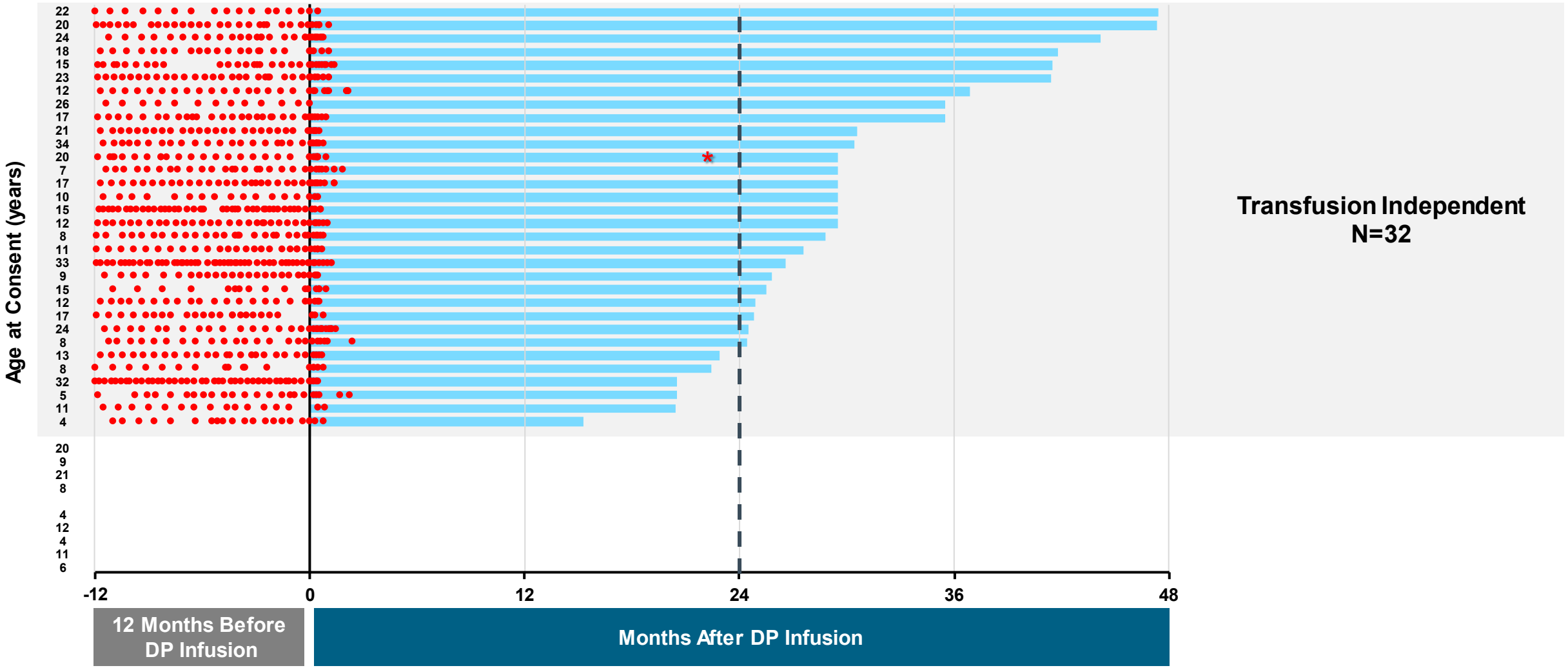


- **Weighted average Hb during TI: 11.5 (9.3 – 13.7) g/dL**

Both Phase 3 Studies Met Primary Endpoint Success Criteria

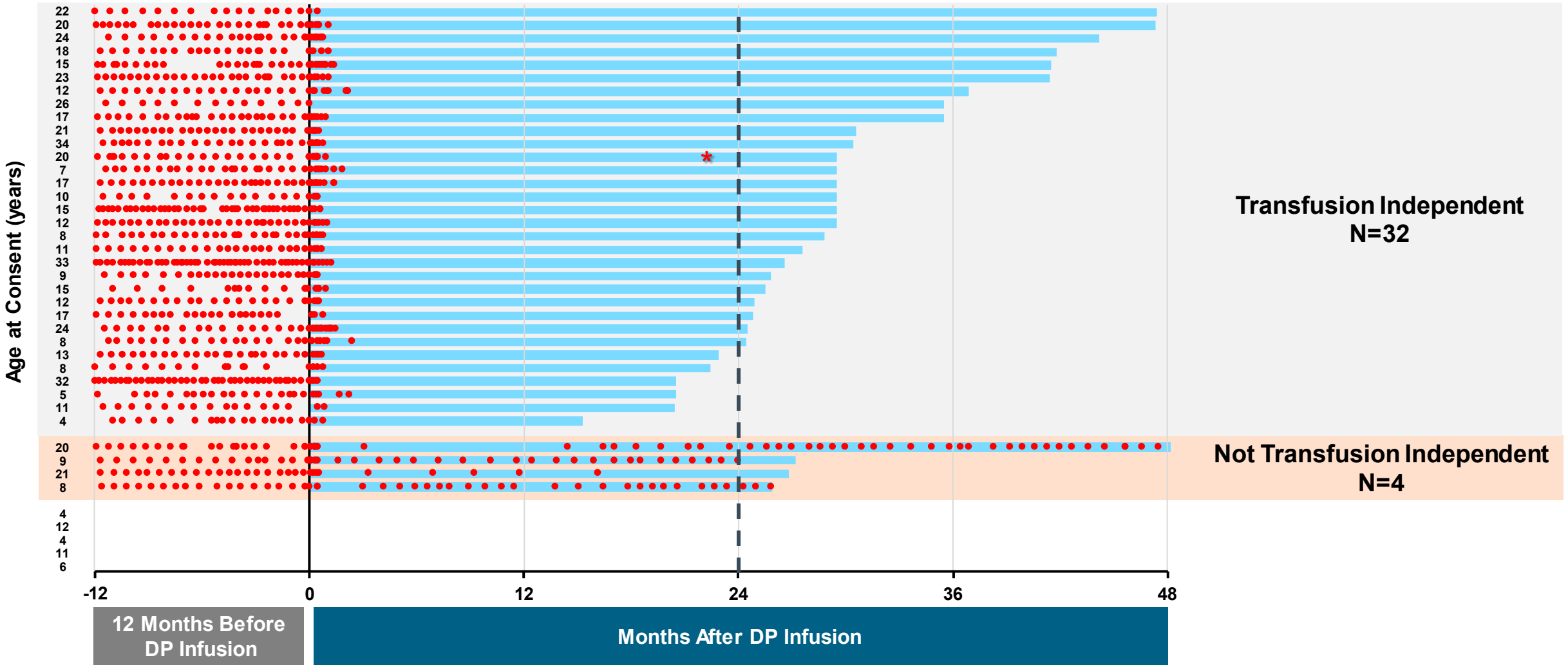
Hb: hemoglobin; TI: transfusion independence; median (min – max) displayed for weighted average Hb during TI

32 of 36 (88.9%) Patients Were Transfusion Independent



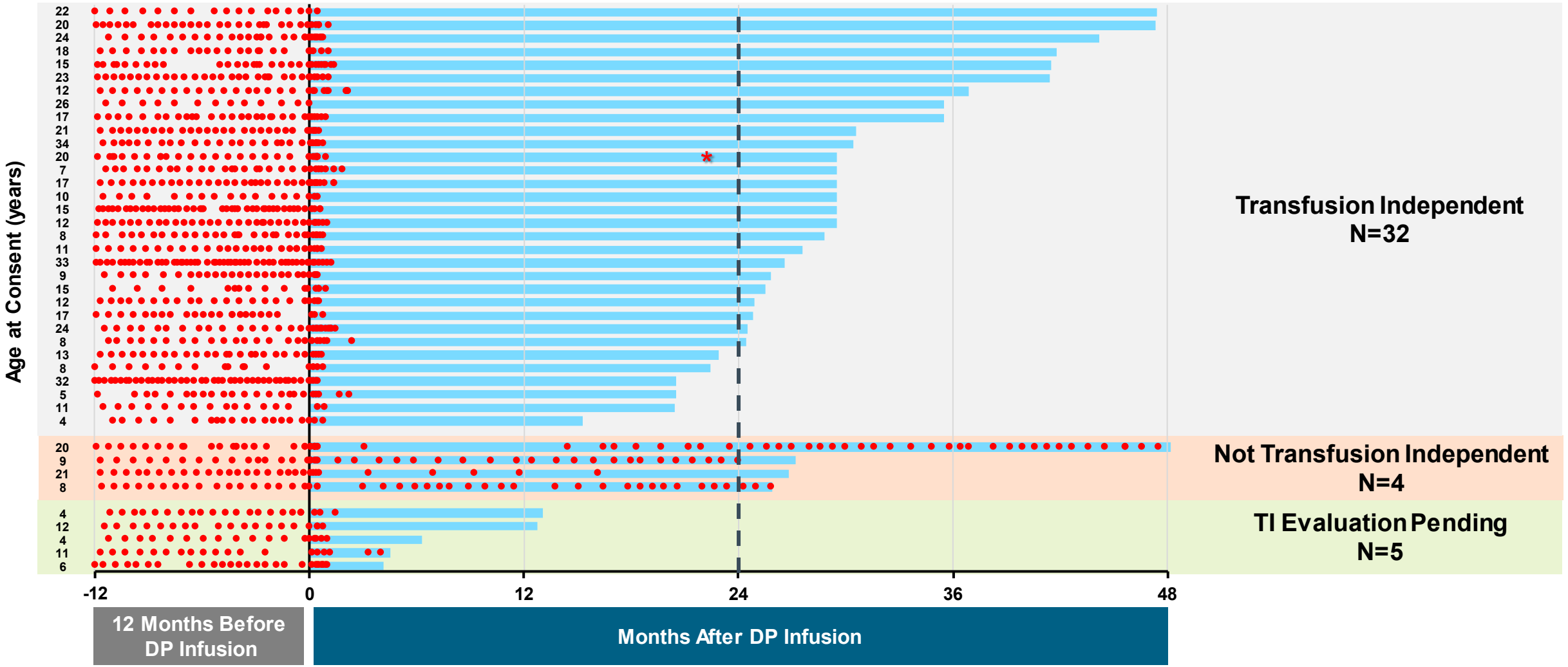
*Patient received acute transfusion for serious blood loss due to orthopedic surgery.
DP: drug product

4 of 36 (11.1%) Patients Were Not Transfusion Independent



*Patient received acute transfusion for serious blood loss due to orthopedic surgery.
DP: drug product

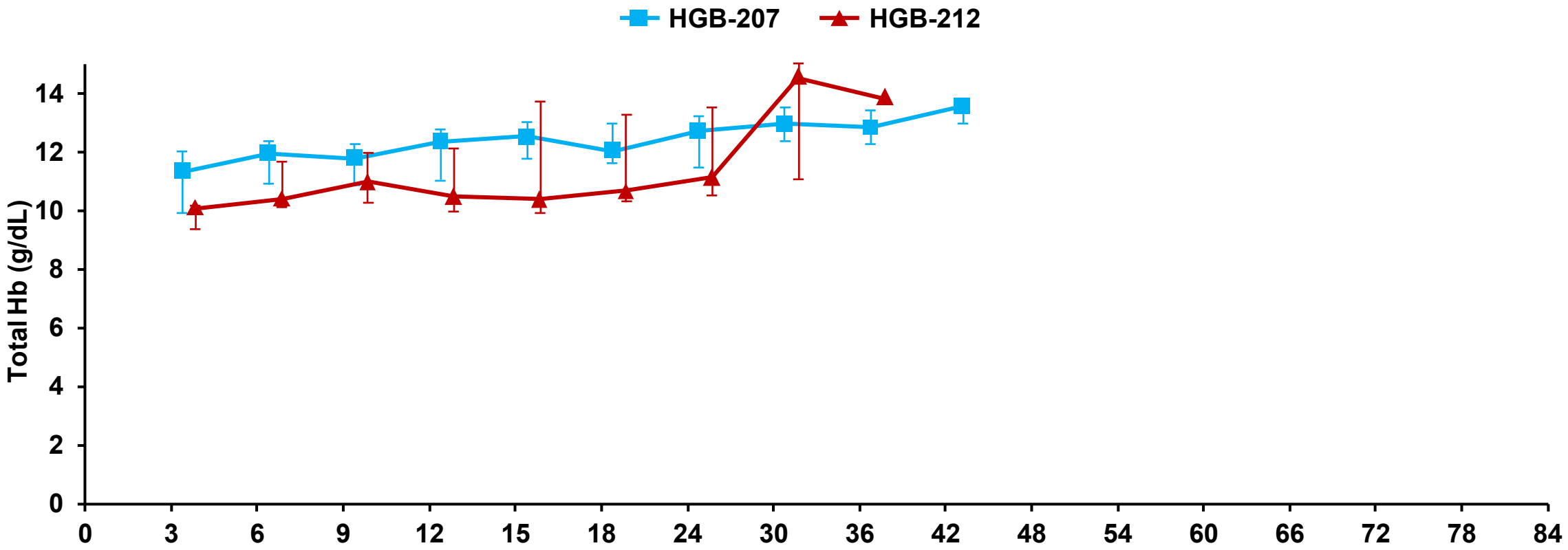
Phase 3 Studies: TI for Up to 4 Years of Follow-up



*Patient received acute transfusion for serious blood loss due to orthopedic surgery.

TI: transfusion independence; DP: drug product

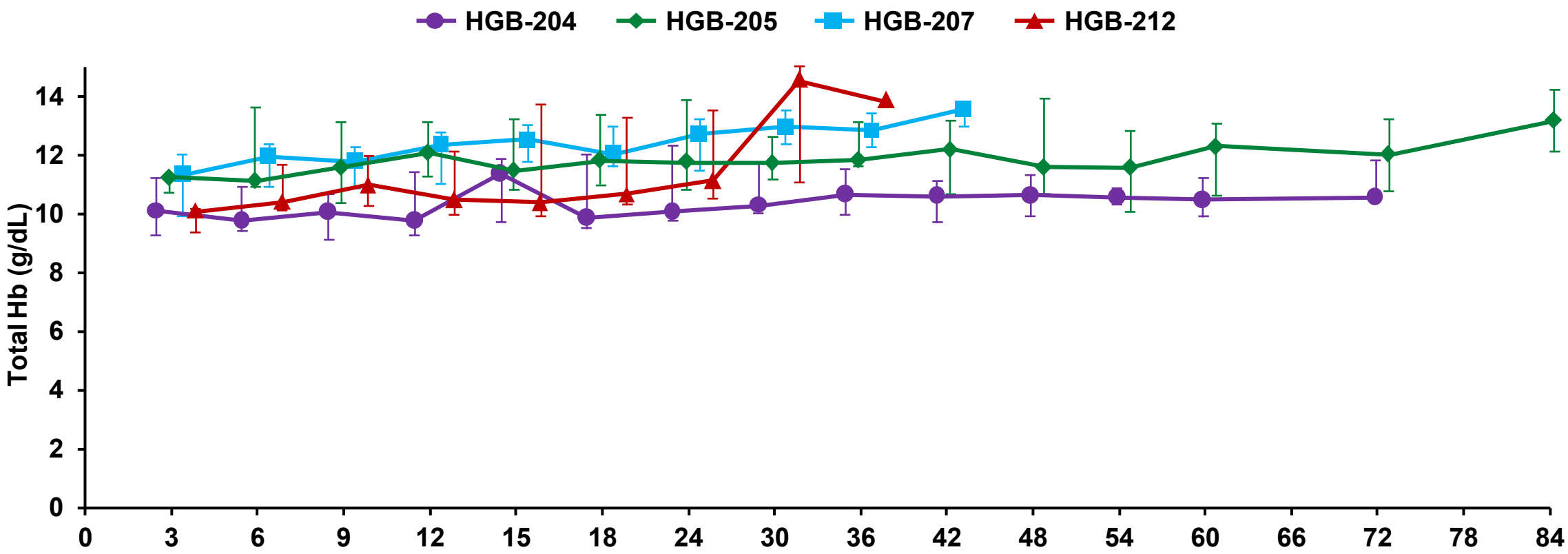
Hemoglobin Durable Up To 7 Years in TI Patients



Number of Patients										
Study HGB-207	12	20	20	19	19	18	17	15	8	5
Study HGB-212	8	12	12	12	9	11	9	3	1	

Median (Q1, Q3) Depicted.
TI: transfusion independence; Hb: hemoglobin; RBC: red blood cell
Unsupported Total Hb represents those without any acute or chronic RBC transfusions within 60 days prior to the measurement

Hemoglobin Durable Up To 7 Years in TI Patients



Number of Patients																	
Study HBG-204	6	9	12	12	9	11	11	12	12	12	12	12	12	-	5	-	-
Study HGB-205	3	3	3	3	3	3	3	3	3	3	3	3	3	-	2	-	2
Study HGB-207	12	20	20	19	19	18	17	15	8	5							
Study HGB-212	8	12	12	12	9	11	9	3	1								

Median (Q1, Q3) Depicted; TI: transfusion independence; Hb: hemoglobin; RBC: red blood cell
Unsupported Total Hb represents those without any acute or chronic RBC transfusions within 60 days prior to the measurement

Most TI Patients Stopped Chelation Therapy

- **Chelation is at physician discretion**
- **To date, over half (30/47, 63.8%) of the patients stopped iron chelation/phlebotomy therapy for at least 6 months post-drug product infusion, of these 30 patients:**
  - Median (min, max) time from stopping chelation to last follow-up was 27.1 (6.0, 56.4) months
  - 12 never restarted chelation, 18 restarted and stopped at a later time
- **11/47 (23.4%) patients had phlebotomy to remove excess iron**

TI: transfusion independence

Summary of Clinical Efficacy

Transfusion Independence

- ~90% of patients achieved near-normal or normal levels of Hb
- Weighted average Hb of 11.5 g/dL without transfusion support
- Adult and pediatric patients of all genotypes
- Durable, expected to be lifelong

Hb: hemoglobin

Benefits of beti-cel Therapy

- Eliminates risk from chronic blood transfusion
- Minimizes reliance on hospital-based transfusions
- Improves erythropoiesis
- Allows patients to stop chelation
- Normalizes iron burden and reduces the potential for organ damage

Safety

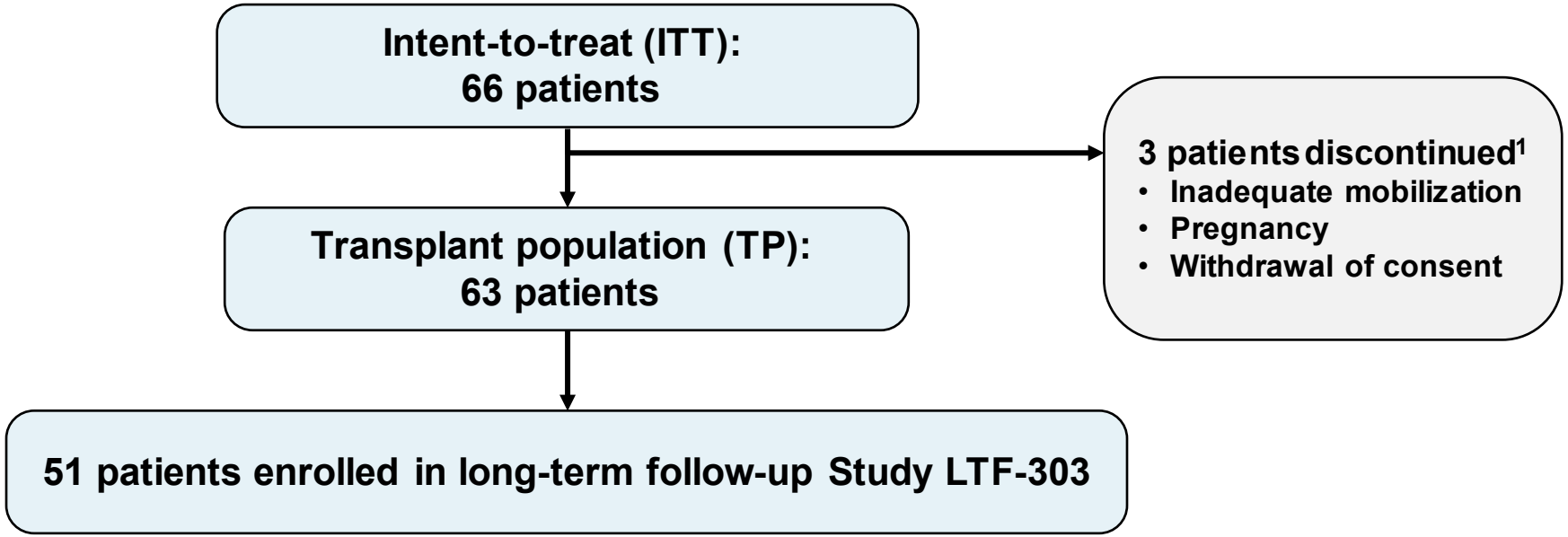
Ajay Singh, MD

Vice President, Pharmacovigilance

bluebird bio, Inc.

63 Patients Contributed to 221.1 Patient-Years of Overall Exposure

Patients with a variety of *HBB* genotypes, sex, and ages across all beti-cel studies were included in the safety analysis



Patients were followed for a median (min, max) of 35.48 (4.1, 86.5) months

Overall exposure: 221.1 patient years

HBB: β-globin gene

[1] Three patients in the ITT population discontinued after 1 cycle of mobilization and were not treated with drug product.

Overview of Safety Presentation

- **Summary of overall safety**
- **Platelet engraftment and recovery**
- **Bone marrow findings**
  - Including cases of interest from sickle cell disease program
- **Recapitulation of vector safety**
- **Observations in FDA briefing book**
- **Plans for pharmacovigilance oversight and long-term follow-up**

Summary of Overall Safety

- **100% overall survival**
- **No cases GVHD**
- **Adverse event profile of regimen:**
  - Largely reflective of conditioning and mobilization/apheresis related events
- **Adverse events related to beti-cel:**
  - Cytopenias and infusion-related events
- **To date no cases of hematologic malignancies**
- **Safety profile similar across genotype and age**
  - Longer engraftment time observed in younger patients

GVHD: graft versus host disease

All Patients Successfully Engrafted

Neutrophil Engraftment Status

Parameter	TP N=63
Achieved neutrophil engraftment, n	63
Time to neutrophil engraftment, median (min, max) days	23.0 (13, 39)

Platelet Engraftment Status

Parameter	TP N=63
Achieved platelet engraftment, n	63
Time to platelet engraftment, median (min, max) days	45.0 (19, 191)

Neutrophil Engraftment (NE): The first of 3 consecutive absolute neutrophil count (ANC) laboratory values obtained on different days ≥0.5 × 10^9/L after a post-transplant value of <0.5 × 10^9/L. Per protocol, NE was considered successful if it occurred by 42 days after drug product infusion (by Day 43)
Platelet Engraftment (PE): Three consecutive platelet values ≥20 × 10^9/L obtained on different days after a post-transplant value of <20 × 10^9/L, with no platelet transfusions administered for 7 days immediately preceding and during the evaluation period
TP: transplant population

Longer Time to Engraftment as Compared to Allo-HSCT in β-Thalassemia

Group/Reference	Neutrophil Engraftment median (min, max) days	Platelet Engraftment median (min, max) days
Bernardo et al. (n=60)	20 (11, 30)	20 (11, 36)
Sellathamby et al. (n=102)	16 (8, 33)	28 (13, 154)
Anurathapan et al. (n=31)	14 (11, 18)	30 (20, 45)
Sun et al. (n=48)	13 (8, 31)	12 (8, 31)
	23 (13, 39)	45 (19, 191)

Comparisons between allo-HSCT and beti-cel may be limited by factors including the donor source. No formal statistical analyses were performed given the historical and retrospective nature of the allogenic data.

Allo-HSCT: allogenic hematopoietic stem cell transplant

Bernardo et al (2012) Blood 120:473–6; Sellathamby et al (2012) Biol Blood Marrow Transplant 18:1219–26; Anurathapan et al (2016) Bone Marrow Transplant 51:813–8; Sun et al (2019) Biol Blood Marrow Transplant 25:1592–1596.

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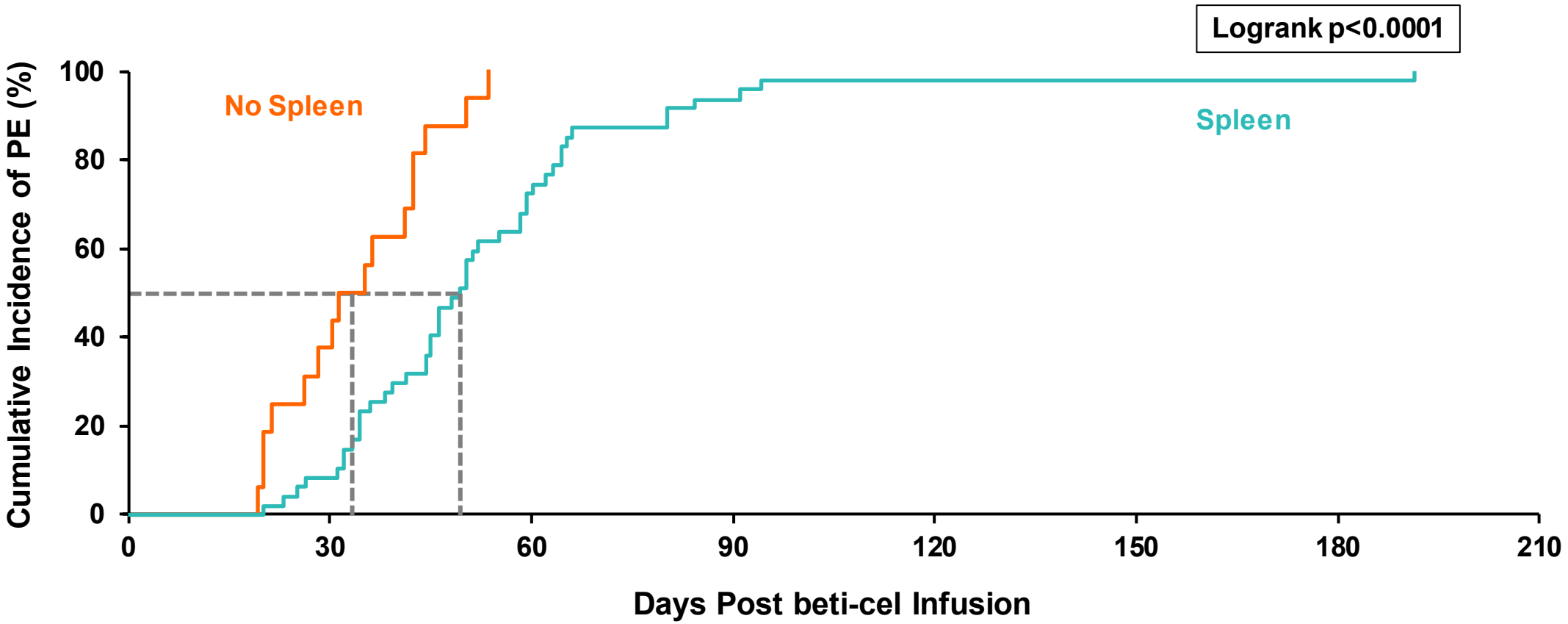
Patients with Spleen had Longer Engraftment Time



Patients at Risk

Spleen	47	43	13	3	1	1	1	0
No Spleen	16	10	0					

Cumulative incidence of platelet engraftment are obtained using the Kaplan-Meier method, where the event is platelet engraftment. Patients who do not have platelet engraftment (PE) are censored at their last contact date (all patients reached PE).
The turquoise line represents median time to PE (for patients without a spleen = 33 days, for patients with spleen = 49 days).

Slower Recovery to Lower Limit of Normal Observed in Patients with Spleen

	Splenectomy N=16	No Splenectomy N=47	TDT N=63
Number of patients whose platelet level returned to lower limit of normal	16	36	52
Time to platelet return to lower limit of normal, median (min, max) days	60.5 (20, 283)	199.0 (46, 2170)	145.5 (20, 2170)

TDT: transfusion-dependent β-thalassemia

Intact Spleen led to Longer Platelet Engraftment Time in Allo-HSCT β-Thalassemia Patients

	Time to Platelet Engraftment (days)	
	Splenectomy	No Splenectomy
beti-cel, median	33	49
Allo-HSCT in β-Thalassemia (Mathews et al.), mean	22.5	32.5

No formal statistical analyses were performed given the historical and retrospective nature of the allogenic data.
Allo-HSCT: allogenic hematopoietic stem cell transplant
Mathews et al (2009) Pediatr Transplant 13:171–6

Delayed Platelet Engraftment is an Identified Risk for beti-cel

- **Time to platelet engraftment is prolonged compared to allo-HSCT**
- **Mechanism is not fully elucidated**
  - Patients with spleen have sluggish recovery of platelets
  - Cryopreservation may impact platelet engraftment times[1]
- **Clinical consequences were limited**
  - One serious case of epistaxis
- **No relation between time to platelet engraftment with bone marrow abnormalities**

Allo-HSCT: allogenic hematopoietic stem cell transplant

[1]Medd et al (2013) Bone Marrow Transplant 48, 243-248

Bone Marrow Collected Routinely in Studies HGB-207 and HGB-212

- **Protocol mandated evaluations**
  - Baseline, Month 12 and Month 24
- **Baseline samples critical**
  - Not routinely collected in β-thalassemia patients
- **Ineffective erythropoiesis in β-thalassemia has been well described**
  - Increase in early erythroid precursors
  - Accelerated erythroid differentiation
  - Maturation blockade at polychromatophilic stage
  - Increase in apoptosis of erythroid precursors

Cao et al (2010) Genetics in Medicine. 2010;12(2); Ribeil et al (2013) The Scientific World Journal, Article ID 394295.

Stress Hematopoiesis at Baseline in beti-cel Patients

- **Variable amounts of erythroid hyperplasia**
  - M:E ratio of 0.3-0.7
- **Erythroid precursors with dysplastic features**
- **Cytoplasmic hemoglobin α-chain inclusions**
- **Ring sideroblasts in variable amounts**
  - Not all baseline samples had iron staining
- **Dysmegakaryopoiesis**

M:E: myeloid:erythroid

Improvement in Erythroid Hyperplasia Following beti-cel Treatment

- **Clear improvement in degree of erythroid hyperplasia**
  - M:E ratio of 0.4-1.2
- **Marked reduction of cytoplasmic inclusions**
- **Morphologic abnormalities**
  - Noted after beti-cel therapy
  - Some improvement in severity of findings

M:E: myeloid:erythroid

Pathology Consistent with Stress Erythropoiesis

- **Overall improvement in erythroid hyperplasia**
- **Evidence of erythroid dysplasia at baseline**
  - No increase after beti-cel infusion
- **No evidence of granulocyte dysplasia**
- **Dysmegakaryopoiesis noted**
  - Noted at baseline (likely reflective of proliferative stress)
  - Similar frequency noted after beti-cel infusion
- **No evidence of MDS or emerging MDS**

MDS: myelodysplastic syndrome

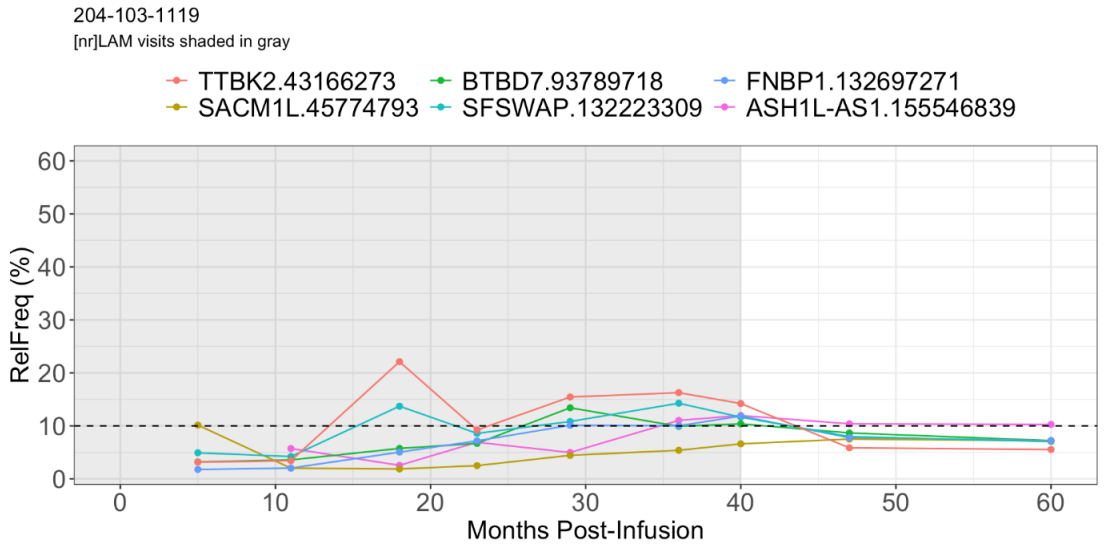
Vector-related Safety

Parameter	n
Patients with ISA results	63
Polyclonal reconstitution	60
Persistent oligoclonality	2
Oligoclonality last visit	1
Patients with RCL results	61
Tested positive for RCL	0

ISA: integration site analysis; RCL: replication competent lentivirus
Persistent oligoclonality: 2 or more consecutive relative frequency results ≥10% for any integration site; Current oligoclonality: last visit was first oligoclonal result

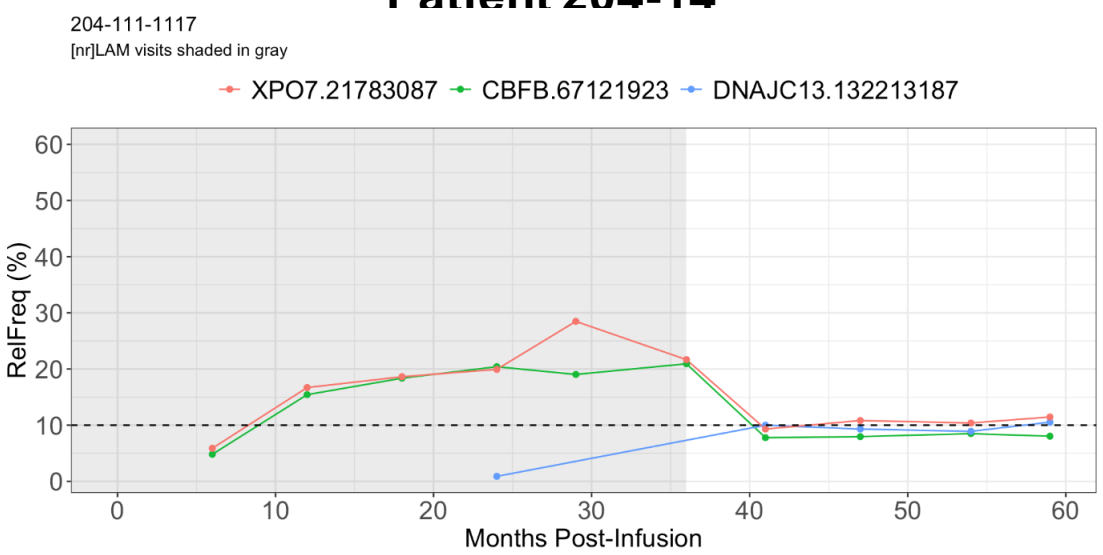
ISA Showing Stable Persistent Oligoclonality

Patient 204-13



Background/Labs/AEs	
Spleen status	Present
NE	Day 18 (neutrophil count 0.632 × 10^9 cells/L)
PE	Day 91 (platelet count 23 × 10^9 cells/L)
Recent CBC (Month 60)	Hb: 10.1 g/L Platelet count: 110 x 10^9/L Leukocytes: 6.3 x 10^9/L

Patient 204-14



Background/Labs/AEs	
Spleen status	Present
NE	Day 24 (neutrophil count 0.837 × 10^9 cells/L)
PE	Day 191 (platelet count 22 × 10^9 cells/L)
Recent CBC (Month 60)	Hb: 10.9 g/L Platelet count: 138 x 10^9/L Leukocytes: 4.9 x 10^9/L

ISA: integration site analysis; AEs: adverse events; NE: neutrophil engraftment; PE: platelet engraftment; CBC: complete blood count; Hb: hemoglobin

No Reports of Insertional Oncogenesis Following Treatment with beti-cel

- **No cases suggestive of LVV-mediated insertional oncogenesis**
- **No other hematologic malignancies**
  - Leukemia
  - Lymphoma
  - Myelodysplastic syndrome

LVV: lentiviral vector

Bone Marrow in SCD Patients Consistent with Stress Erythropoiesis

- **Two patients treated with lovotibeglogene autotemcel**
- **Both β^S/β^S with two α-globin gene deletions**
- **Both presented with anemia, one patient also presented with neutropenia (transient grade 2)**
- **Morphologic abnormalities in erythroid line (dysplasia/dyserythropoiesis) noted**
  - Raised possibility of MDS
- **Transient gain of chromosome 8 by FISH, normal karyotype**
- **No driver mutations on NGS**

SCD: sickle cell disease; MDS: myelodysplastic syndrome; FISH: fluorescence in situ hybridization; NGS: next generation sequencing

Clinicopathological Picture Does Not Suggest MDS in SCD Patients with Two α-Globin Gene Deletions

- **No evidence of clonal process**
  - ISA: highly polyclonal reconstitution
  - NGS: unremarkable
- **Pathology evaluation**
  - Stress erythropoiesis
  - Not suggestive of MDS
- **Overall picture: similar to patients with β-thalassemia**
  - α/β-globin imbalance
- **Patients are clinically stable**

ISA: integration site analysis; NGS: next generation sequencing; MDS: myelodysplastic syndrome

Overall Summary of Key Safety Issues

Safety Issue	Comments
Delayed platelet engraftment	Key role of spleen Cryopreservation: theoretical contribution
No evidence of hematologic malignancy	Bone marrow evaluations consistent with underlying β-thalassemia
No evidence of insertion oncogenesis	beti-cel (N=63) BB305 LVV (N=113)
Majority patients had polyclonal reconstitution	VAMP4: common insertion site (Rel freq <0.25%) Not an identified proto-oncogene Not associated with cell proliferation or survival

LVV: lentiviral vector; Rel Freq: relative frequency

Overall Assessment and Risk Mitigation

Safety Issue	Comments/Risk Mitigation
Key Safety Topics	
Delayed platelet engraftment	Identified risk Communication: Labeling and qualified treatment centers education
Bone marrow abnormalities	Consistent with stress erythropoiesis in β-thalassemia
Vector safety	Patients with oligoclonality: enhanced surveillance bluebird bio: facilitate ISA, as clinically indicated, post-marketing and routinely in registry
Potential Risks Based on Mechanism of Action	
Insertional oncogenesis	No cases: continued surveillance required
Other Risks	
Long term risks of interest for gene therapy	No cases of interest: continued surveillance required

ISA: integration site analysis

bluebird bio has Robust Long-Term Follow-up Measures

	Long Term Follow-up Study (LTF-303)	Registry Study (REG-501)
Patient population	Patients treated in all clinical trials	Patients treated in post-marketing setting
Type of study	Interventional	Non-interventional
15-Year follow-up post infusion	✓	✓
Adverse events including malignancy[1]	✓	✓
CBCs	✓	✓
ISA	✓	✓[2]
RCL	Event-driven	Event-driven
Transfusions	✓	✓

[1] Serious adverse events, adverse events of interest, and drug product related adverse events.
[2] Requested, not mandated.
CBCs: complete blood counts; ISA: integration site analysis; RCL: replication competent lentivirus

Overall Safety Conclusion

- **Safety profile, to date, supports favorable benefit/risk for beti-cel**

- **bluebird bio remains fully committed**
  - Ensuring transparent communication of identified and emerging risks
  - Robust long term pharmacovigilance activities to provide FDA and prescribers with valuable long term safety data

Benefit:Risk

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Unmet Need for a Potentially Curative Treatment Option for Patients

STOP
transfusions with near-normal or normal total hemoglobin levels

PREVENT
the life-shortening complications of β-thalassemia

REDUCE
need for life-long disease-specific monitoring

Why beti-cel?

- **beti-cel appears to be an important option with a positive benefit:risk profile**
  - Achieve transfusion independence, reduce iron load and improves quality of life
  - No risk for GVHD, graft failure, and graft rejection
- **beti-cel is intended for patients who are suitable for transplant irrespective of age and donor status, thus expanding treatment options to a broader patient population**

GVHD: graft versus host disease.

Clear and Clinically Meaningful Benefit

- **Great majority of patients achieved transfusion independence, across all phases of clinical studies, all ages, and all genotypes**
  - 88.9% have achieved TI in Phase 3
  - The median weighted average Hb during TI was 11.52 (9.3, 13.7) g/dL in Phase 3
  - Durable TI with up 7 years of follow-up across all studies

- **Trends of erythropoiesis improvement were observed**
  - Myeloid to erythroid ratios improved
  - Bone marrow morphology improved
  - Markers of anemia improved

- **Some patients have used phlebotomy after beti-cel infusion and many patients have stopped iron chelation**

TI: transfusion independence; Hb: hemoglobin.

Safety Profile

- 63 patients were treated with beti-cel and followed for 4 months to 7 years, with overall exposure of 221 patient-years
- The safety profile of the overall treatment regimen (i.e., mobilization, conditioning, and beti-cel infusion) largely reflects known effects of plerixafor, G-CSF, and busulfan
- No immunological complications typical of allo-HSCT were seen
- Malignancy, including LVV-mediated insertional oncogenesis, and vector-derived RCL were not observed

G-CSF: granulocyte-colony stimulating factor; allo-HSCT: allogeneic-hematopoietic stem cell transplantation; LVV: lentiviral vector; RCL: replication competent lentivirus.

Patient and Family Considerations

- **Benefits of treatment**
  - May achieve lifelong transfusion independence and Hb levels near-normal or normal
  - May discontinue chelation therapy
- **Potential risks associated with treatment**
  - Delayed platelet engraftment
  - Insertional oncogenesis and malignancy
  - Infertility due to myeloablative conditioning
- **Long-term follow-up recommended in the commercial setting, including in drug product registry REG-501**

Hb: hemoglobin.

Case History with beti-cel #1

18-year-old with HbE β-thalassemia

Before beti-cel

- Started transfusions late (>10 years of age) after developing growth delay and early bony changes
- Did not have suitable HLA donor

After beti-cel

- Transfusion independent 7+ years
- Completing PhD in biomedical engineering
- International travel

HbE: hemoglobin E, HLA: human leukocyte antigen.

Case History with beti-cel #2

4-year-old with β^0/β^0 β-thalassemia

Before beti-cel

- Diagnosed by newborn screening, began chronic transfusions at 6 months of age
- Parents almost immediately inquired about curative options
- Preimplantation genetic diagnosis and *in vitro* fertilization used to conceive healthy sibling, not HLA-matched

After beti-cel

- Last transfusion at Day +30
- HbA^{T87Q} and Total Hb at Month 6: 9.3 and 10.5 g/dL
- Completed kindergarten, currently in first grade

HLA: human leukocyte antigen; Hb: hemoglobin.

Potential to Cure Patients with β-Thalassemia who Require Regular RBC Transfusions

beti-cel has the potential to cure patients with β-thalassemia who require regular RBC transfusions

ACROSS

- **All ages**
- **Non-β^0/β^0 and β^0/β^0 genotypes**
- **Sex**
- **Race**

by increasing functional HbA and total Hb to near normal or normal levels and eliminating dependence on chronic RBC transfusion

beti-cel clinical studies demonstrate clear and clinically meaningful benefit with an acceptable safety profile for patients

RBC: red blood cell; HbA: adult hemoglobin; Hb: hemoglobin.