Exa-cel for the Treatment of Sickle Cell Disease (SCD) in Patients ≥ 12 Years With Recurrent Vaso-Occlusive Crises (VOCs)

October 31, 2023

Cellular, Tissue, and Gene Therapies Advisory Committee

Vertex Pharmaceuticals

Introduction

Stephanie Krogmeier, PhD

Vice President, Global Regulatory Affairs

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Proposed Indication for Exa-cel

For the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises (VOCs)

Severe SCD: Serious, Rare, Debilitating, Life-Shortening Genetic Disorder Affecting Hemoglobin Function

- ~20,000 people in US have severe disease defined by recurrent vaso-occlusive crises (VOCs) and are candidates for transplant therapy
- In the US, ~90% of people with SCD are from African descent

- Clinical hallmark of severe SCD is recurrent painful VOCs; acute and chronic organ complications leading to significant morbidity and mortality
- No broadly available curative options; high unmet need

Exa-cel: A Nonviral, One-Time Autologous CRISPR-Edited Cellular Treatment

- Development of exa-cel is grounded in human genetics showing that fetal hemoglobin (HbF) can substitute for sickle hemoglobin (HbS) and eliminate VOCs

- Permanent, irreversible, and precise edit results in the reduction of *BCL11A* gene transcription which leads to an increase in levels of HbF

- Consistent with this mechanism and site of action, comprehensive non-clinical studies demonstrate no off-target editing by exa-cel

Exa-cel Clinical Development Program Overview

SCD Pivotal
Phase 1/2/3
Study 121
Ongoing

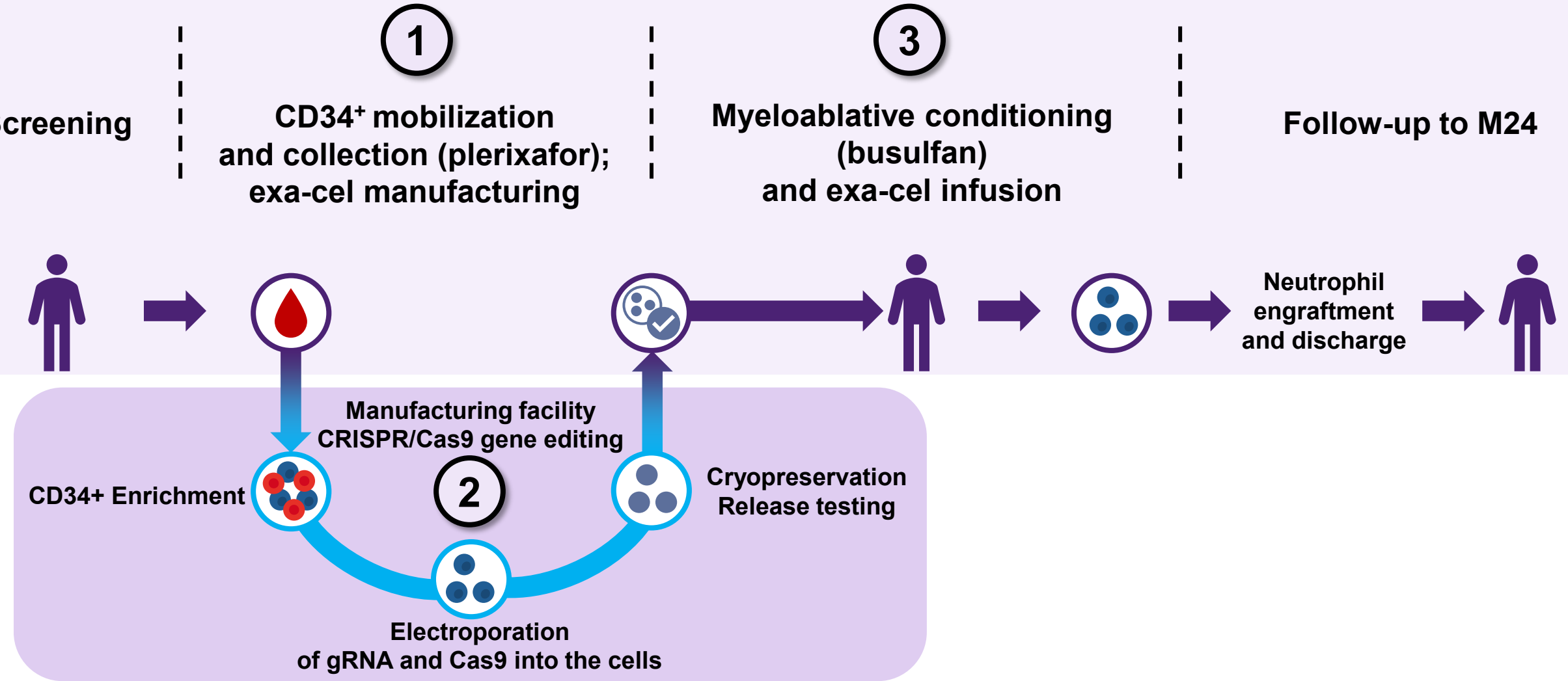
- N = 44 dosed (data cutoff 14 June 2023), including 12 adolescents
- Patients with severe SCD 12 – 35 years old
- Efficacy and safety for 2 years after exa-cel infusion

LTFU
Phase 3
Study 131
Ongoing

- N = 17 enrolled (of 46 total patients)
- Patients dosed with exa-cel in Study 121
- Long-term safety and efficacy 15 years after exa-cel infusion

Designed in consultation with the Agency, including sample size of ~ 45 patients; Study 121 has completed enrollment and dosing of all patients, 46 patients in total, including 12 adolescents

Study 121 Patient Journey and Exa-cel Manufacturing



Exa-cel Demonstrated Transformational Clinical Benefit

Efficacy

- VF12: Absence of VOCs for at least 12 consecutive months; 29 of 30 (97%) of patients achieved VF12, including 6 adolescents
- HF12: Free from inpatient hospitalization for VOCs sustained for at least 12 consecutive months; 30 of 30 (100%) of patients achieved HF12, including 6 adolescents

Non-Clinical Safety

- Comprehensive non-clinical safety package in support of the exa-cel program
- Design of exa-cel minimized potential for off-target risk, and evaluation did not identify any evidence of off-target editing by exa-cel

Clinical Safety

- Generally safe and well tolerated
- Safety profile consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk
- No clinically significant differences in the safety profile for adult and adolescent patients

Agenda

Unmet Need	**Alexis Thompson, MD, MPH** Division Chief, Hematology Children's Hospital of Philadelphia
Efficacy	**William Hobbs, MD, PhD** Vice President, Clinical Development, Hematology Vertex Pharmaceuticals
Non-Clinical Safety	**David Altshuler, MD, PhD** Executive Vice President and Chief Scientific Officer Vertex Pharmaceuticals
Clinical Safety	**Christopher Simard, MD** Vice President, Global Patient Safety Vertex Pharmaceuticals
Clinical Perspective	**Haydar Frangoul, MD** Medical Director, Pediatric Hematology/Oncology and Cellular Therapy Sarah Cannon Research Institute

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Vertex Pharmaceuticals

Jaime Rubin Cahill, MA, MPH
Vice President, Health Economics and Outcomes Research
Vertex Pharmaceuticals

Unmet Need

Alexis Thompson, MD, MPH

Division Chief, Hematology

Children’s Hospital of Philadelphia

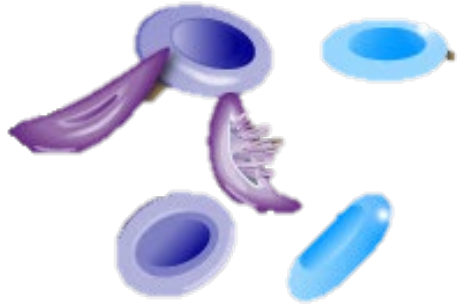
Severe Sickle Cell Disease is Rare

- ~ 100,000 cases reported within US[1-5]
  - ~ 20,000 have severe disease defined by recurrent VOC, considered for transplant therapy
- Occurs at disproportionately high rates among individuals of African descent in the US[2,6,7]
  - Middle Eastern, Mediterranean, Indian/Asian descent also affected
  - Communities with high unmet medical need
  - Areas of low income and healthcare disparities

1. Lubeck et al. 2019; 2. Lee et al, 2019 3. Desai et al. 2020; 4. Shah et al. 2020; 5. Shah et al. 2019; 6. NORD, 2023; 7. CDC, 2019

Sickle Cell Disease Results in Recurrent VOCs and Progressive Organ Failure

Sickle cell disease caused by mutation in β-globin gene

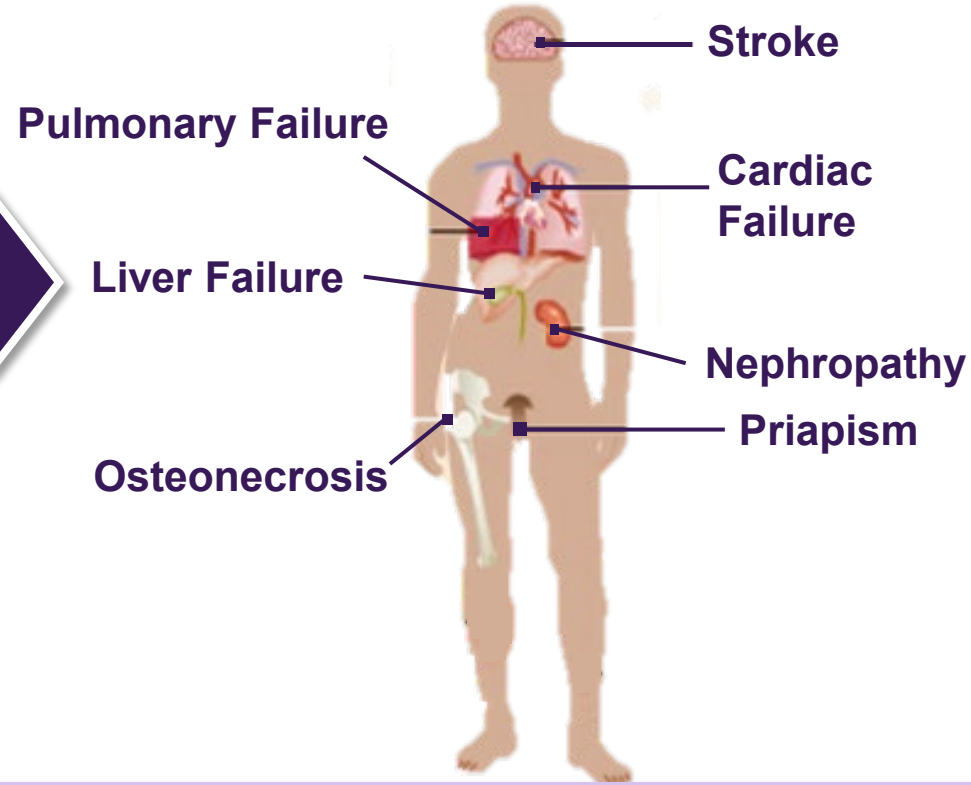


- Chronic Anemia
- Hemolysis of cells with no or insufficient HbF

Recurrent VOC

- Severe, acute pain
- Acute chest syndrome
- Priapism
- Splenic sequestration

Progressive End Organ Damage

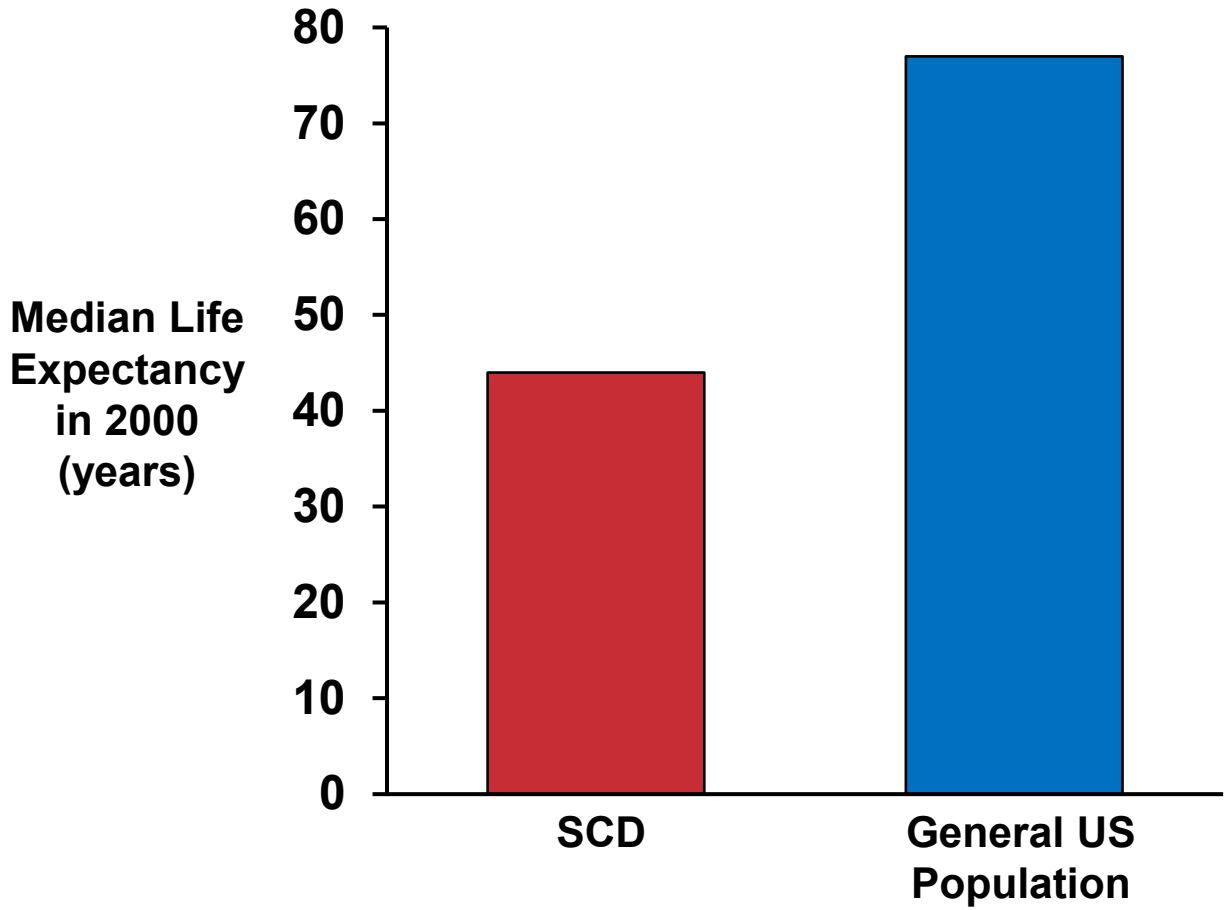


Frequent VOC decrease QoL and can lead to psychosocial consequences

Right Figure modified from Akinseye, 2011

VOCs Associated With Increased Hospitalizations and Mortality Risk

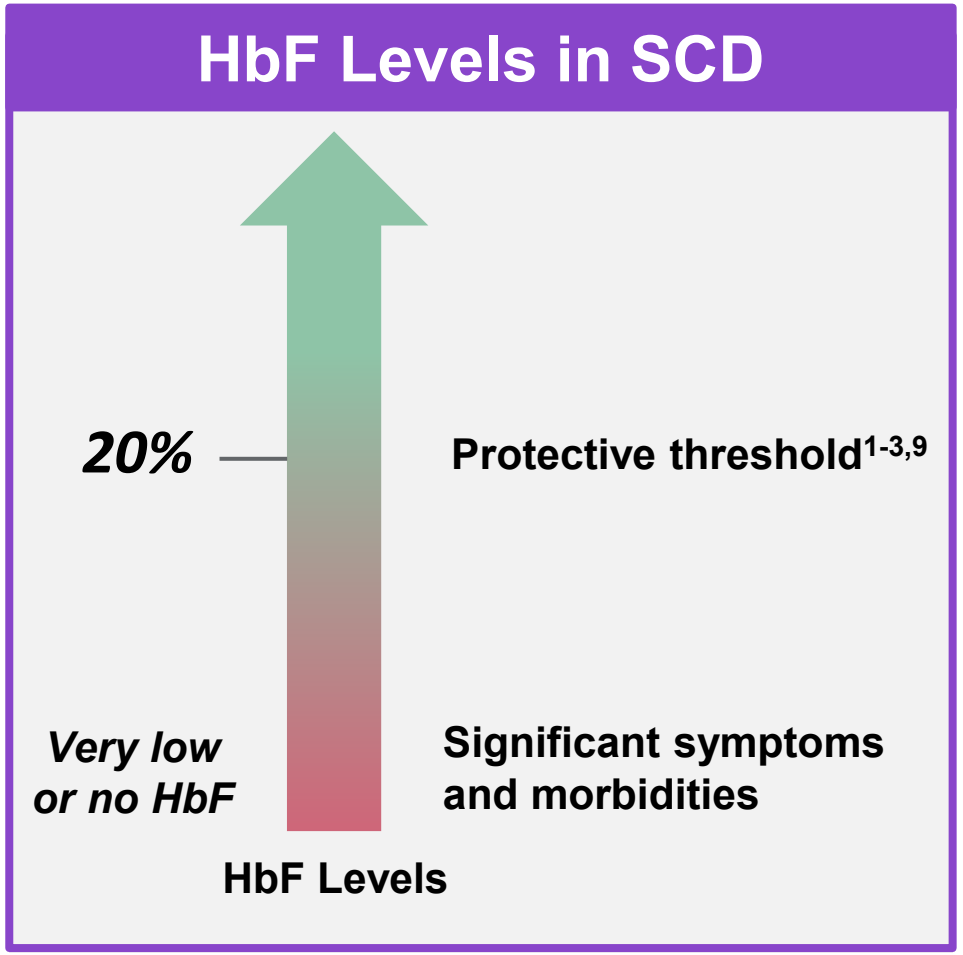
- VOCs are the most common cause of hospitalizations for SCD patients[1-5]
  - ~ 100,000 per year in US
  - Hospitalizations for VOC associated with increase mortality risk
- Overall survival of SCD patients is reduced by 20-30 years[6-9]
- No broadly available curative options that eliminate VOCs; high unmet need



1. Ballas et al. 2005; 2. Shah et al. 2019; 3. Piel Hematologica et al. 2017; 4. Fingar et al. 2019; 5. Darbari et al. 2013; 6. Lubeck et al. 2019; 7. Platt et al. 1994; 8. Elmariah et al. 2014; 9. Thein 2017

HbF: Established as Powerful Modulator of Clinical and Hematologic Features of SCD[1-4]

- Elevated levels of HbF result in improved morbidity and mortality[1-7]
- Protection from elevated HbF demonstrated by natural history
  - Neonates / infants with SCD become symptomatic when HbF synthesis declines[8]
  - Patients who have co-inherited hereditary persistence of HbF[1-3]



1. Akinsheye et al. 2011; 2. Steinberg, 2012; 3. Ngo, 2012; 4. Steinberg, 2020; 5. Bailley 1992; 6. Castro et al 1994; 7. Platt, 1994; 8. Sankaran et al. 2013; 9. Powars, 1984

Summary of Unmet Need in Sickle Cell Disease

- Sickle cell disease is rare, debilitating, and life-shortening
- Patients suffer with painful VOCs that cause
  - Chronic complications across multiple organs
  - Significant impairment in daily life, quality of life, and lifespan
- HSCT is curative, but with limited availability and significant complications
- Current medical treatments not curative and do not eliminate VOCs
- Durable therapy that raises HbF would provide important option

Patients and families need curative medicine for sickle cell disease

Efficacy

William Hobbs, MD, PhD

Vice President of Clinical Development, Hematology

Vertex Pharmaceuticals

Exa-cel SCD Clinical Development Program Demonstrates Transformational Clinical Benefit

Study 121 Pivotal Study
- 2 year follow-up after exa-cel infusion

Study 131 Long Term Follow-up Study
- 15 year follow-up after exa-cel infusion

The study met the primary and key secondary endpoints:
- VF12: Proportion of patients who have not experienced any VOC for ≥ 12 consecutive months
- HF12: Proportion of patients free from inpatient hospitalization for VOCs for ≥ 12 consecutive months

Clinical benefit was consistent across the patient population including adolescent and adult age groups

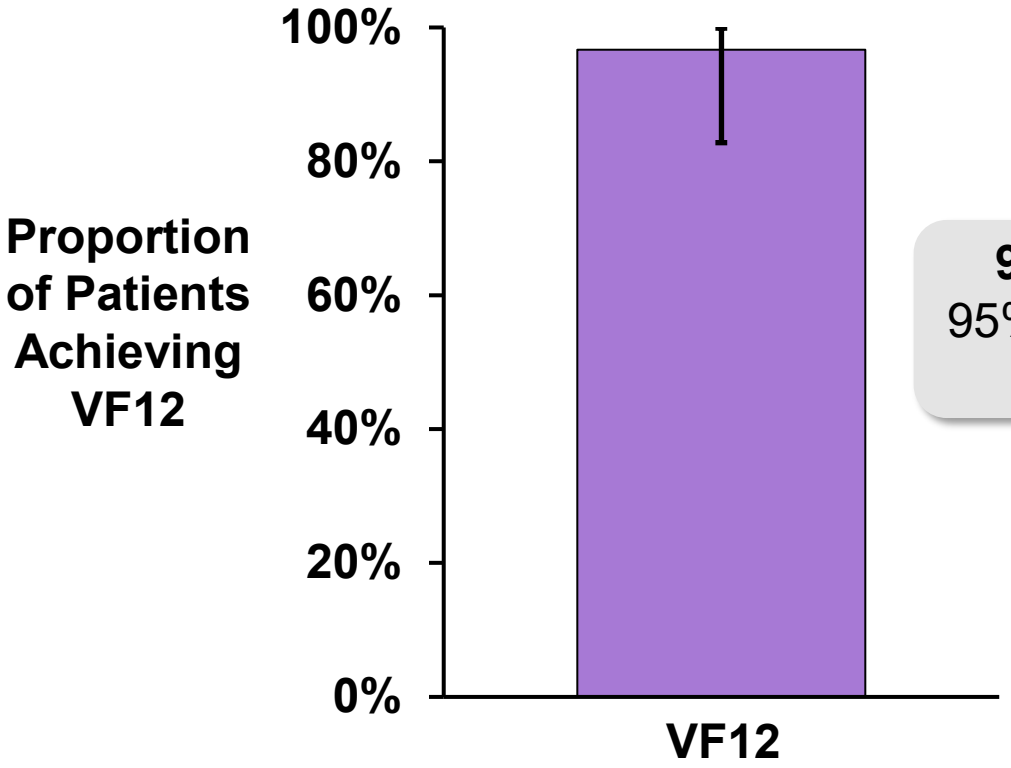
Clinical benefit was durable, with maximum follow-up of over 4 years

Patient Characteristics for Study 121

	Primary Effiacy Set (PES) N = 30	Full Analysis Set (FAS) N = 44
Age at screening (years), **mean** (sd)	**22** (6.0)	**21** (6.1)
12 – 17 years	**20%**	**27%**
18 – 35 years	**80%**	**73%**
Annualized rate of VOCs, mean (range)	**3.9** (2.0, 9.5)	**4.1** (2.0, 18.5)
Annualized rate of inpatient hospitalization for VOCs, mean (range)	**2.7** (0.5, 8.5)	**2.7** (0.5, 9.5)
Annualized duration of inpatient hospitalizations for VOCs (days), mean (range)	**17.1** (2.0, 64.6)	**19.7** (2.0, 136.5)

Patients Treated With Exa-cel Achieved Clinically Meaningful and Statistically Significant Achievement of VF12

Primary Endpoint: VF12



96.7% (29/30)
95% CI: 82.8, 99.9
$p < 0.0001$

Secondary Endpoint

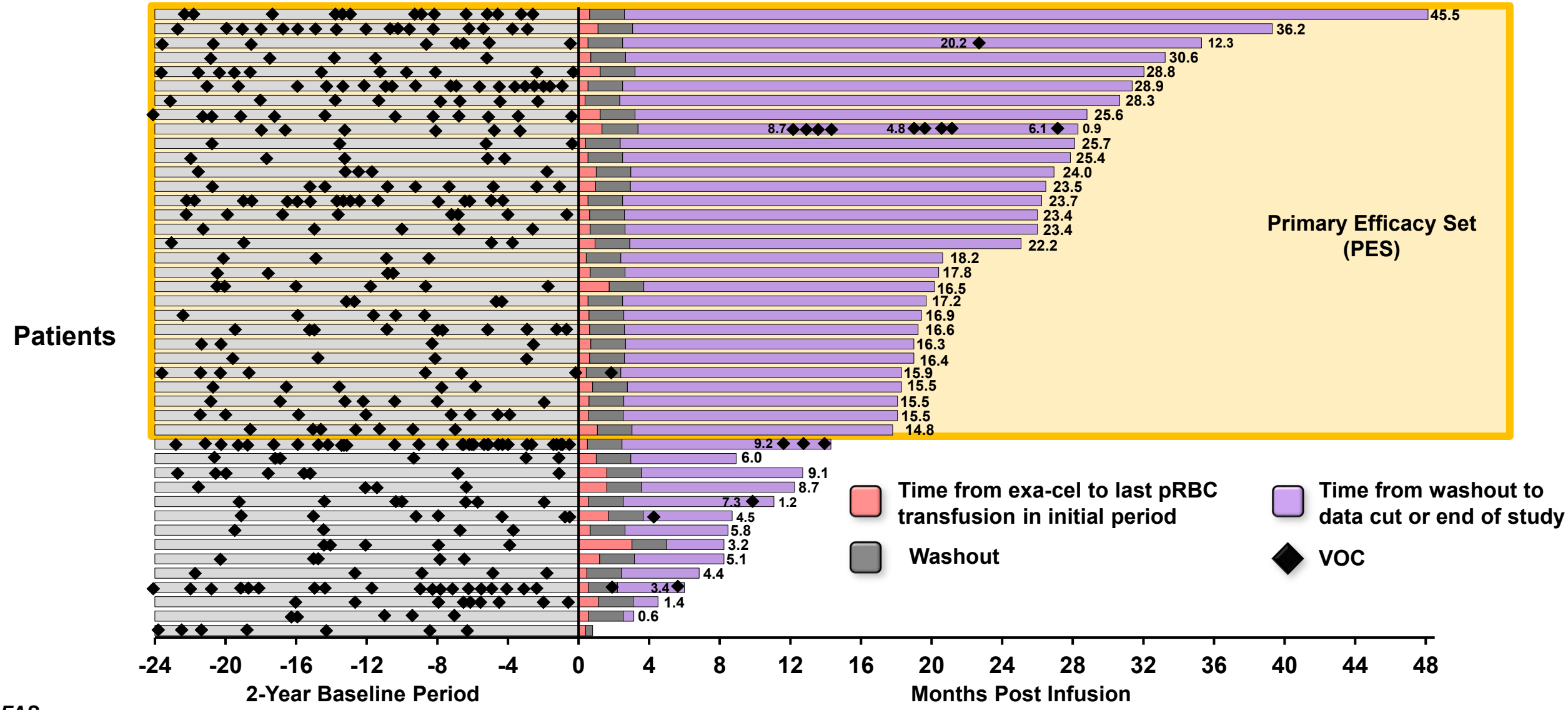
VOC free duration

Mean: 22.4 months

Range: [14.8, 45.5 months]

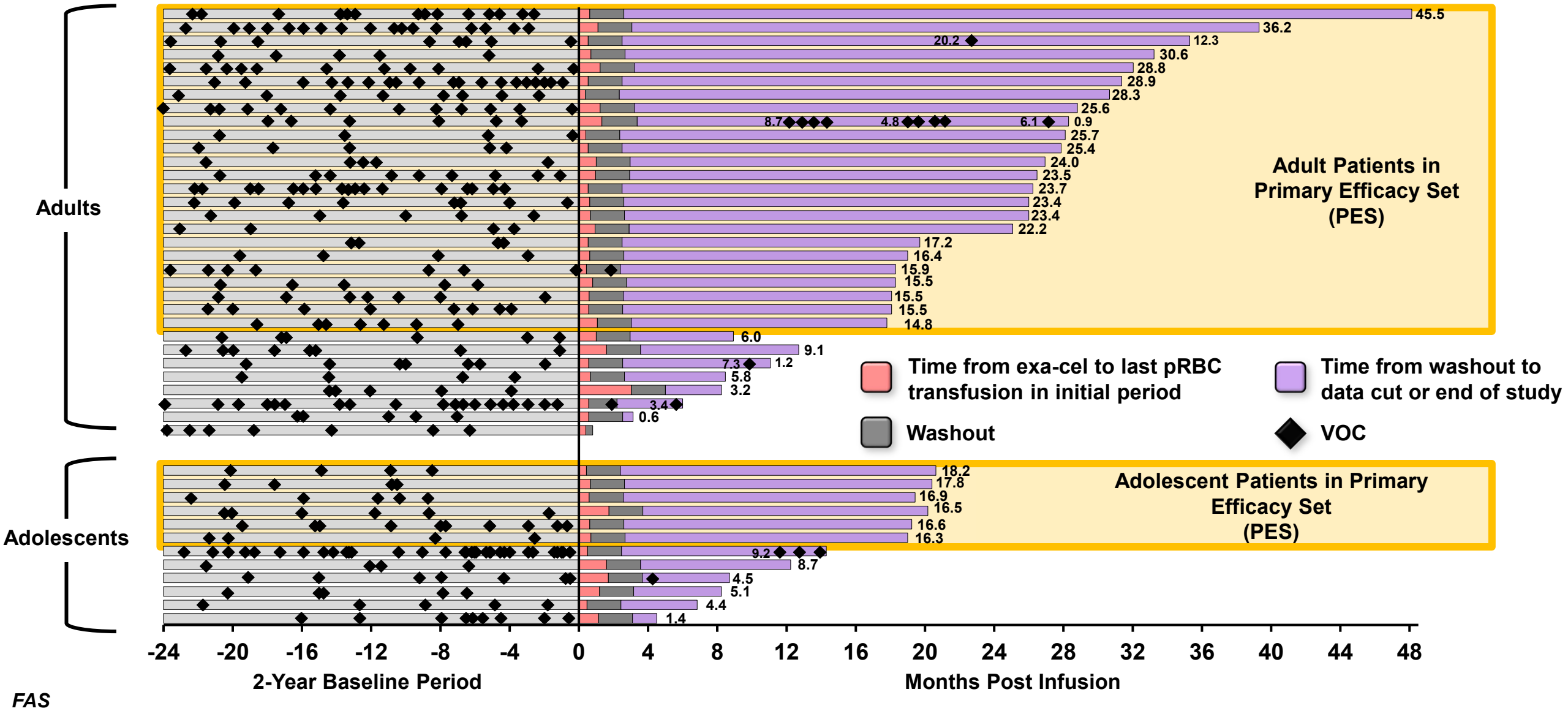
PES

Patients Treated With Exa-cel Achieved Clinically Meaningful and Durable Benefit Free From VOCs



FAS

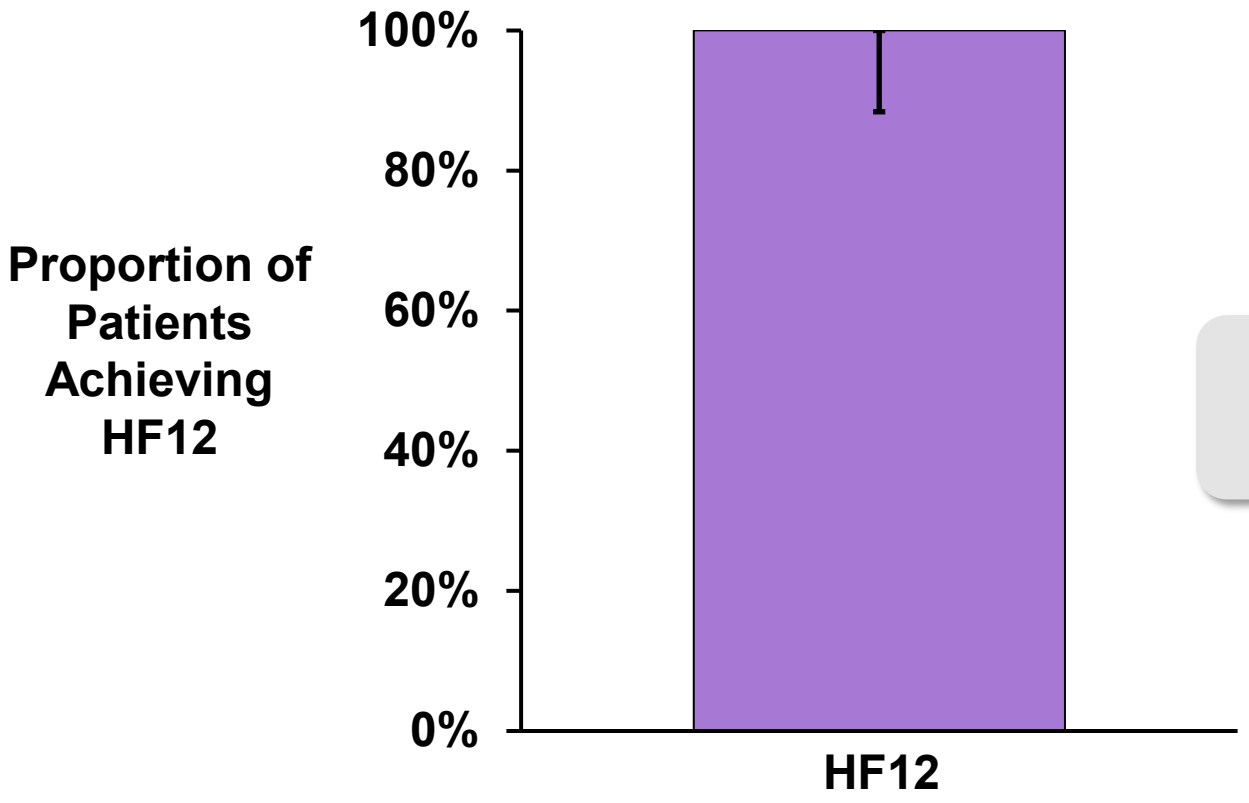
Consistent Efficacy and Clinically Meaningful Benefit Between Adults and Adolescents



FAS

Patients Treated With Exa-cel Were Free From Inpatient Hospitalization for VOC

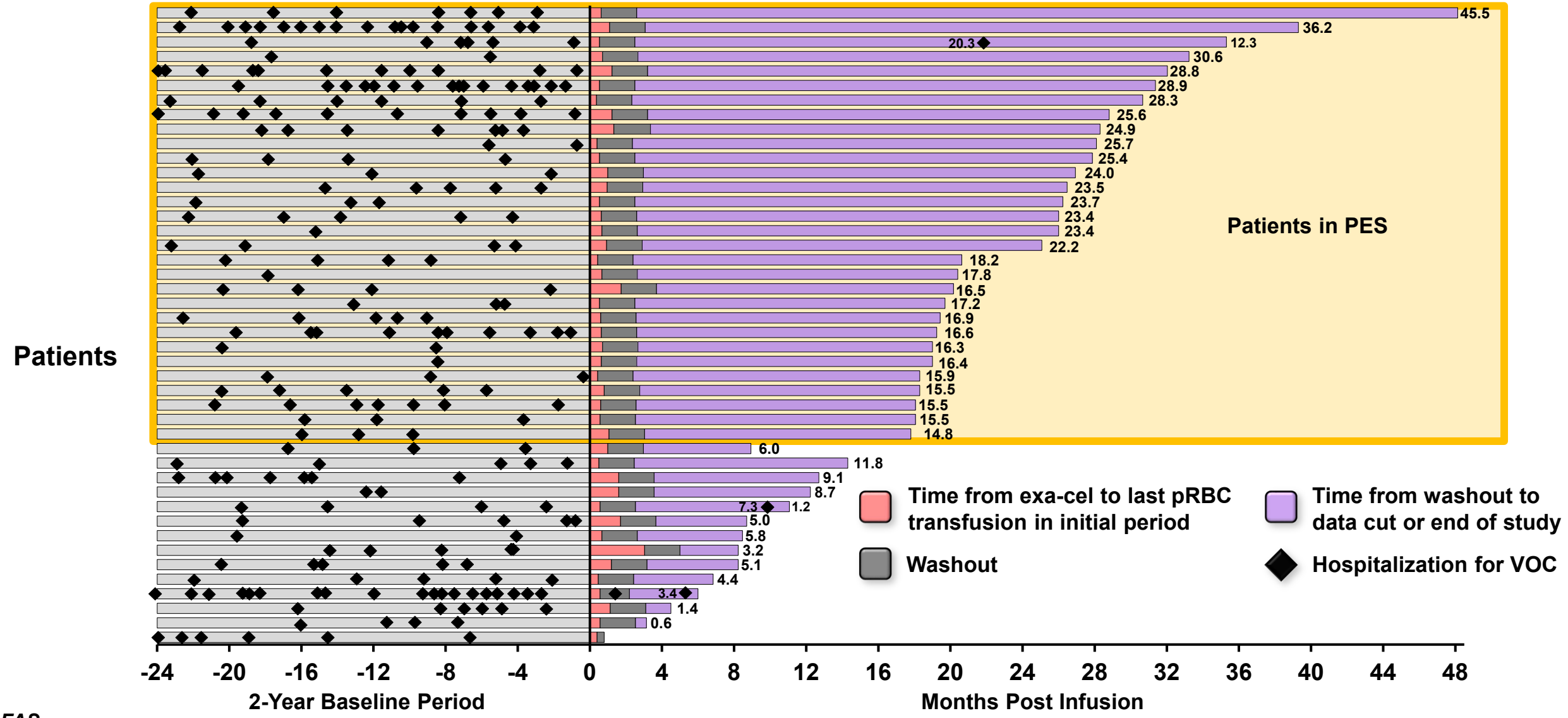
Key Secondary Endpoint: HF12



100% (30/30)
95% CI: 88.4, 100
$p < 0.0001$

PES

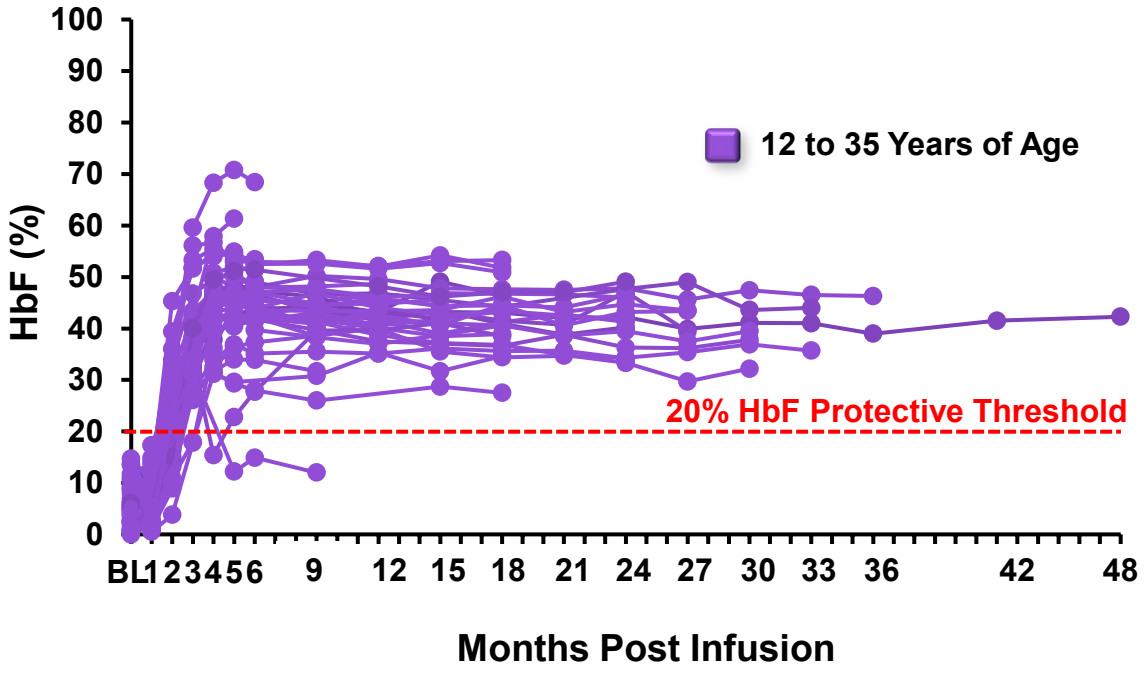
Exa-cel Exhibited Durable Effect in Avoiding Inpatient Hospitalizations Due to VOCs



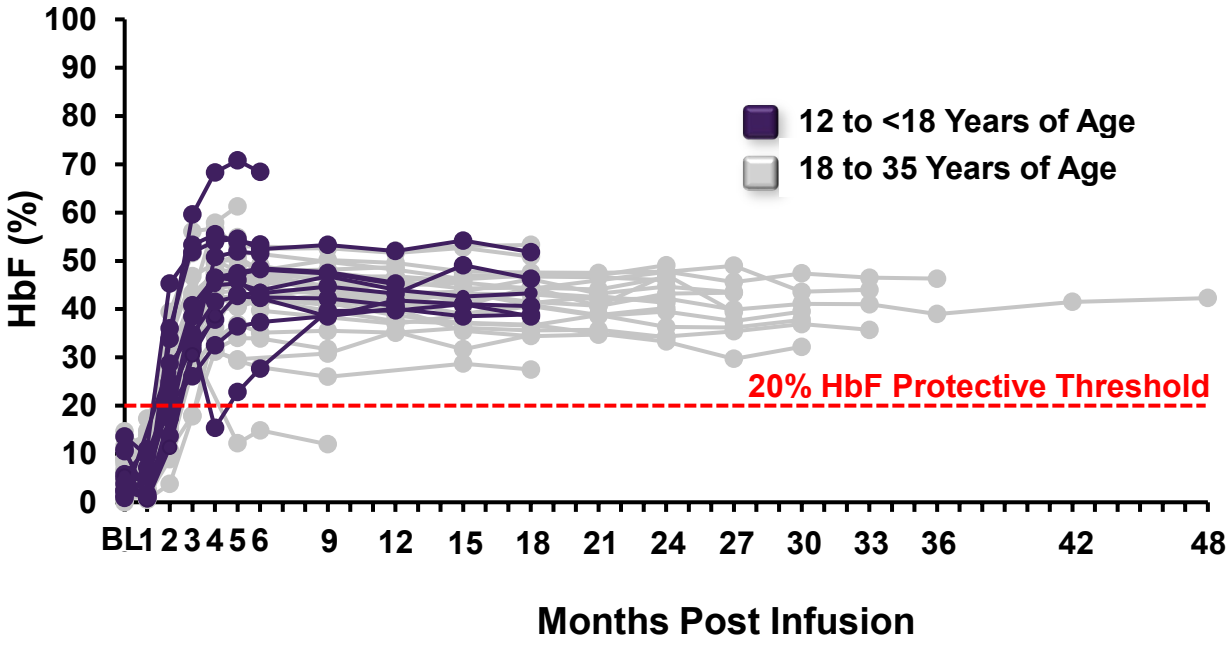
FAS

Exa-cel Achieved Rapid, Robust, and Durable Levels of HbF% ≥ 20% in Adults and Adolescents

All Patient Increases in HbF %



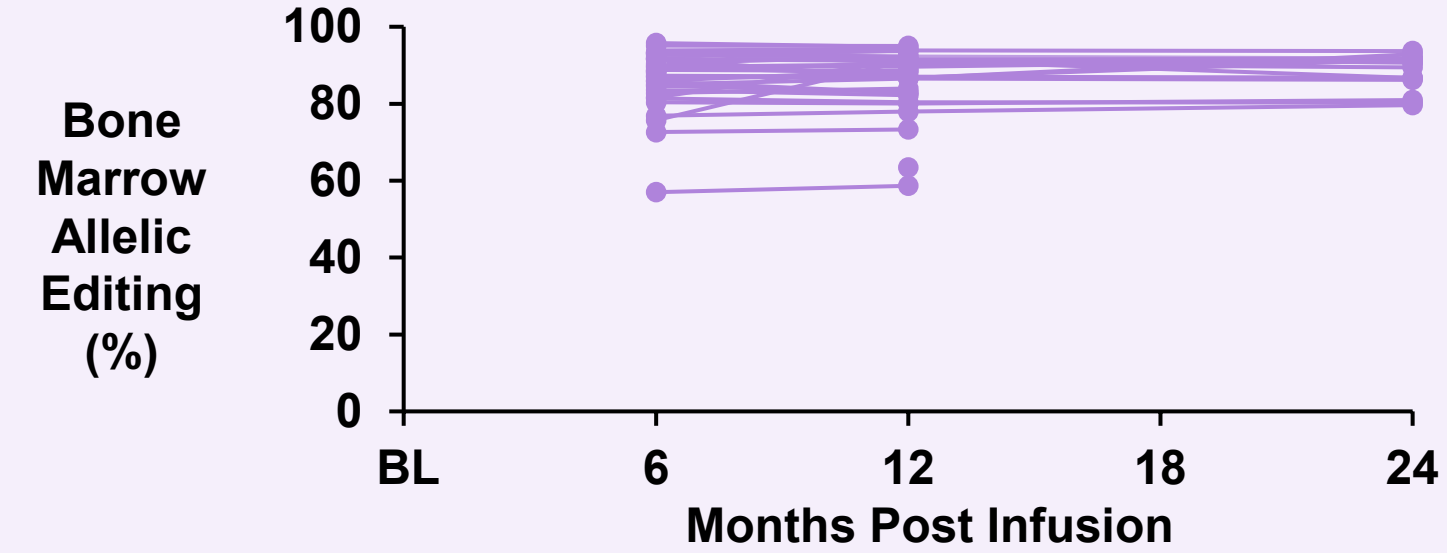
Adolescent Increases in HbF % Consistent with Adults

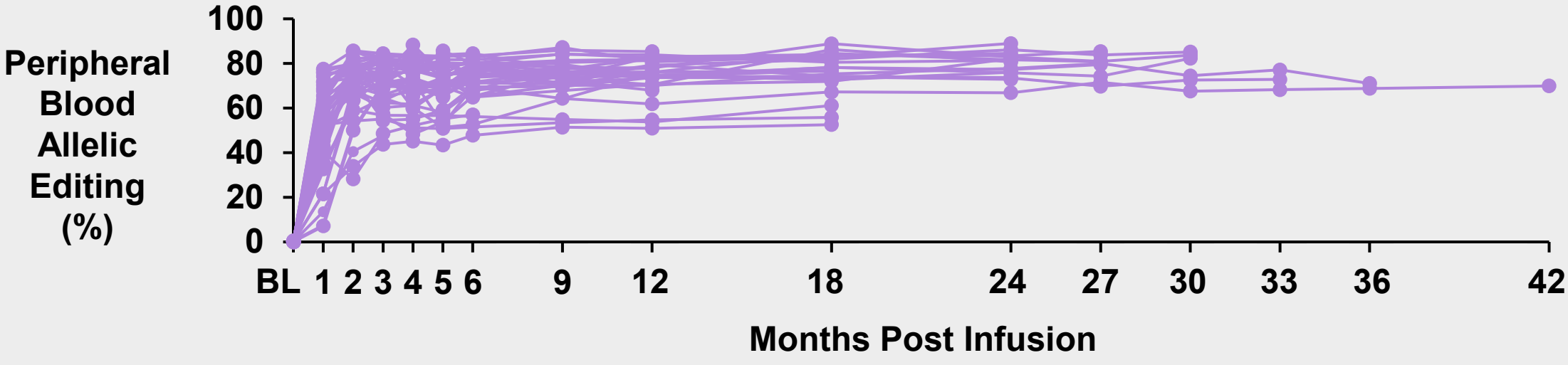


BL: baseline

FAS

Bone Marrow and Peripheral Blood Allelic Editing Durable Through Follow-up and Indicates Long-Term Meaningful Benefit After Exa-cel





BL: baseline; FAS

Exa-cel Demonstrated Transformational Durable Clinical Benefit in Patients With Severe SCD

- **97% achieved ≥ 12 consecutive months without a VOC**
- **100% achieved ≥ 12 consecutive months free from inpatient hospitalization for VOC**

- Efficacy consistent across all endpoints and subgroups
  - Efficacy in adolescent patients is similar to adults
- Efficacy durable over time
  - Mean VOC-free duration was 22.4 months (range: 14.8 to 45.5 months)
  - Rapid, robust, and durable increases in HbF levels
  - Stable allelic editing over time in bone marrow and peripheral blood

Non-Clinical Safety

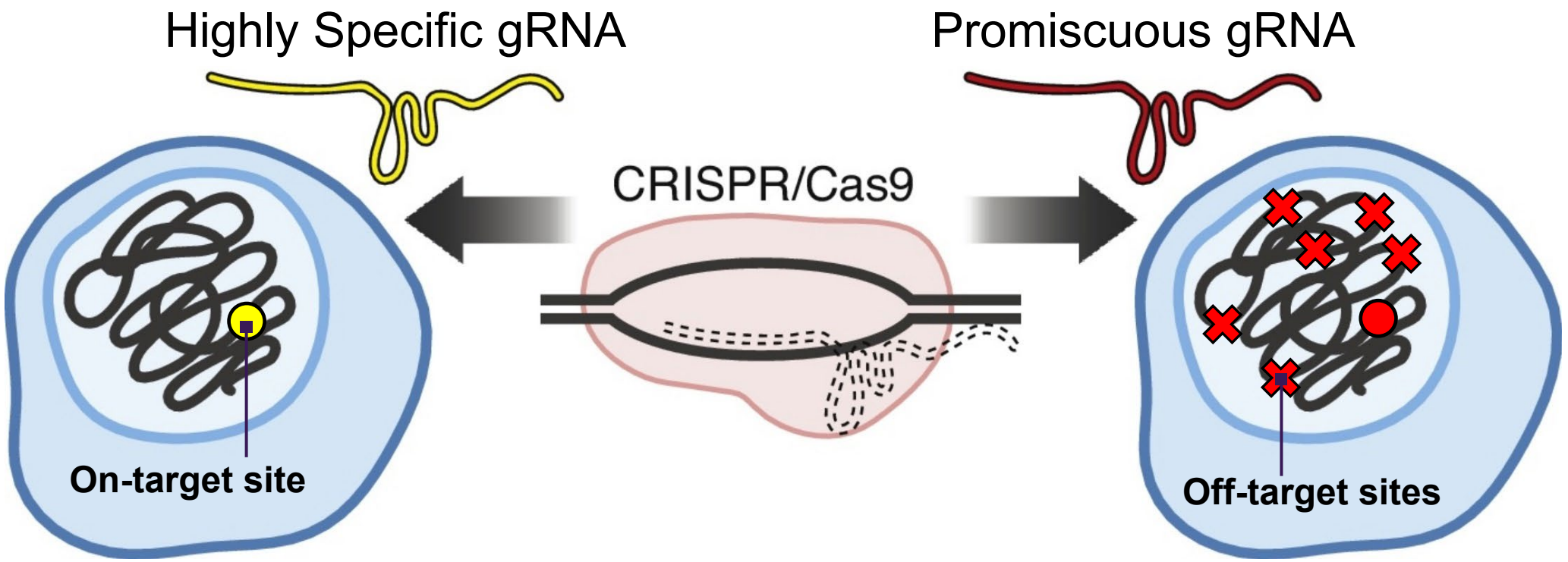
David Altshuler, MD, PhD

Executive Vice President and Chief Scientific Officer
Vertex Pharmaceuticals

Summary: Key Non-Clinical Results That Inform Risk Due to Gene Editing

On-target editing	On-target edits limited to erythroid specific enhancer
Chromosomal analysis	No evidence of chromosomal abnormalities
Off-target editing	No evidence of off-target editing
Carcinogenicity	No evidence of tumorigenicity in GLP mouse toxicity study
Biodistribution	Editing did not impact distribution and persistence of cells post-transplant

Background: Specificity of CRISPR Editing is Determined by Uniqueness of On-Target Site and guide RNA (gRNA)



For editing to occur, genomic site must match gRNA sequence and also include an active Protospacer Adjacent Motif (PAM)

Adapted from: Current Opinion in Chemical Biology Volume 29, December 2015, Pages 72-78

Strategies to Minimize Off-Target Risk by Exa-cel

Design of exa-cel to minimize risk of off-target editing

- *Ex vivo* editing to limit CRISPR exposure
- On-target site with unique sequence
- Screened candidates to select specific gRNA

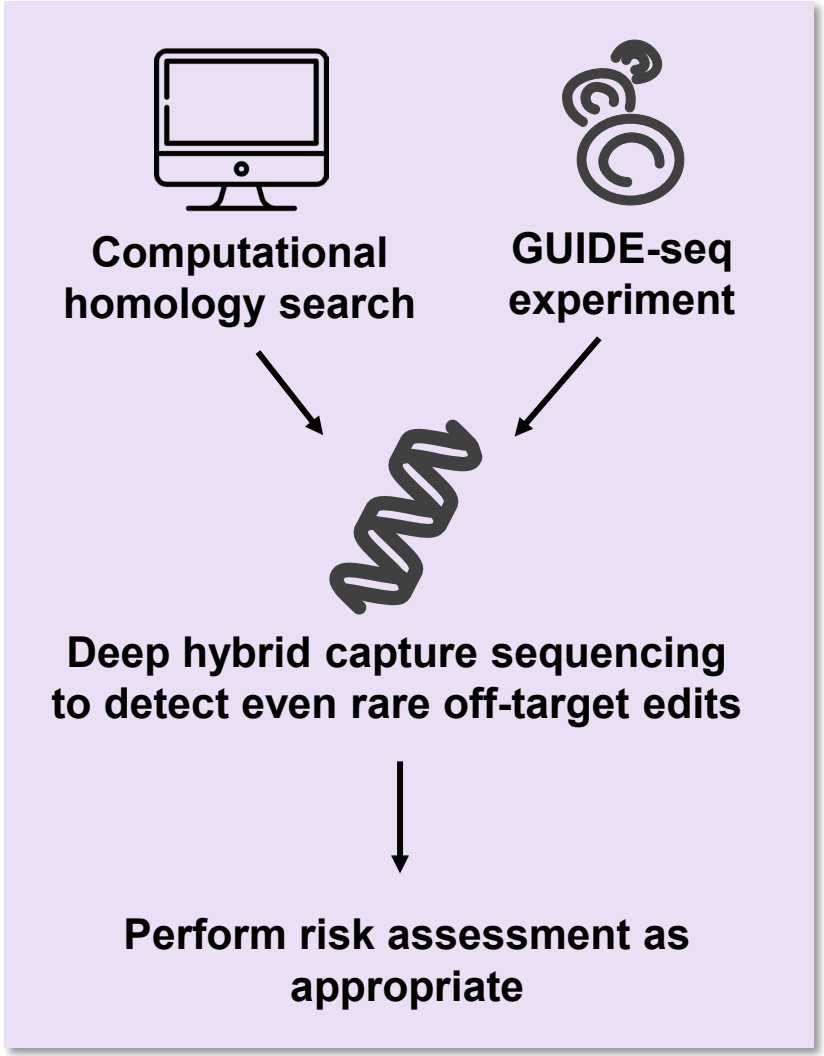
Evaluation of potential off-target editing by exa-cel

- Methods of off-target analysis
- Evaluation of sites based on genetic diversity
- Performed risk assessment

Conclusion: design of exa-cel minimized potential for off-target risk, and evaluation did not identify evidence of off-target editing by exa-cel

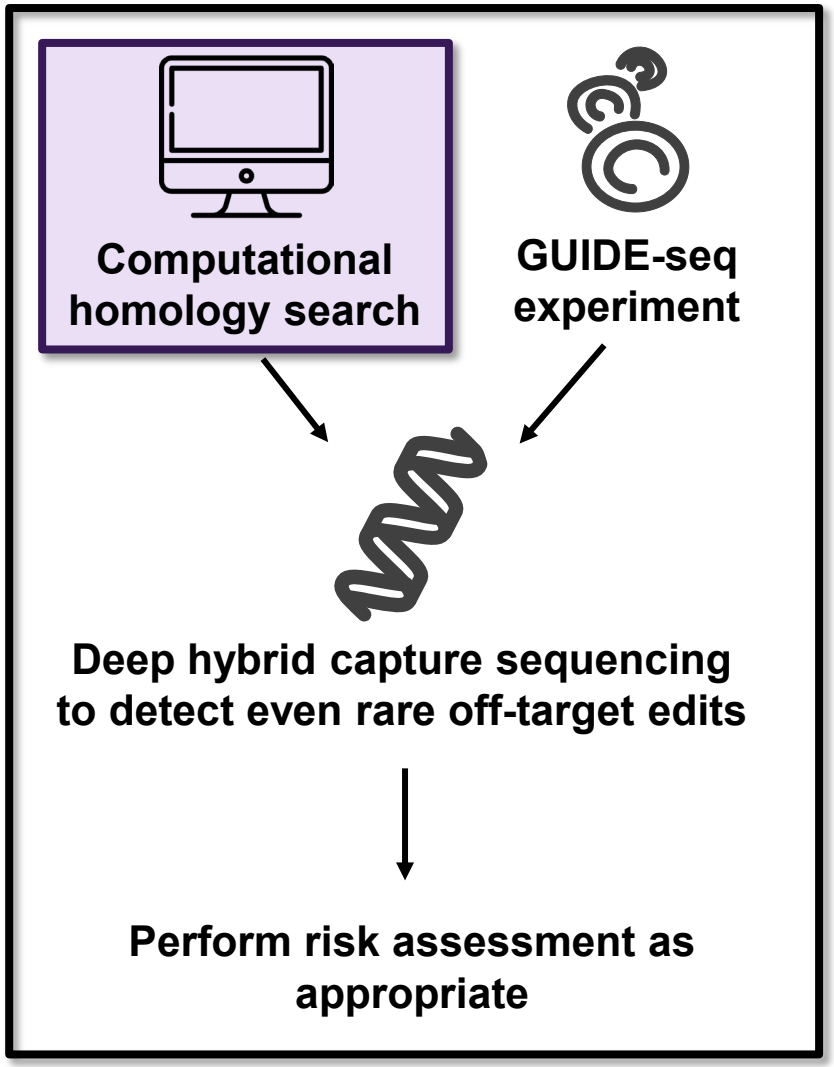
Framework for off-target evaluation

Framework: Evaluating Potential for Off-Target Editing



- **Nominated** candidate sites with potential for off-target editing using **two orthogonal, genome-wide methods**
  - Included information from **human genetic diversity** relevant to the target exa-cel patient population
- **Evaluated** for off-target edits at all nominated sites in edited and unedited CD34+ cells using **high coverage, hybrid capture** next-generation sequencing
- **Performed risk assessment** for any sites if confirmed with off-target edit, or if low frequency variant not tested directly

Nomination: Computational Homology Search



- We performed a **computational homology search**[1,2,3] of the human genome reference sequence including alternative PAMs

		PAM
On-target site	CTAACAGTTGCTTTTATCAC	NGG
Candidate off-target site	TTAACAGCTGCCTTTATCAC	TGC

- Study #1: Broad search incorporated up to 5 mismatches, or 2 mismatches with a bulge, and **nominated 5,007 candidate sites**
- Study #2: focused search (≤3 mismatches, 2 mismatches with a bulge), nominated **171 candidate sites**
- Study #3: added **50 additional sites** based on genetic variation

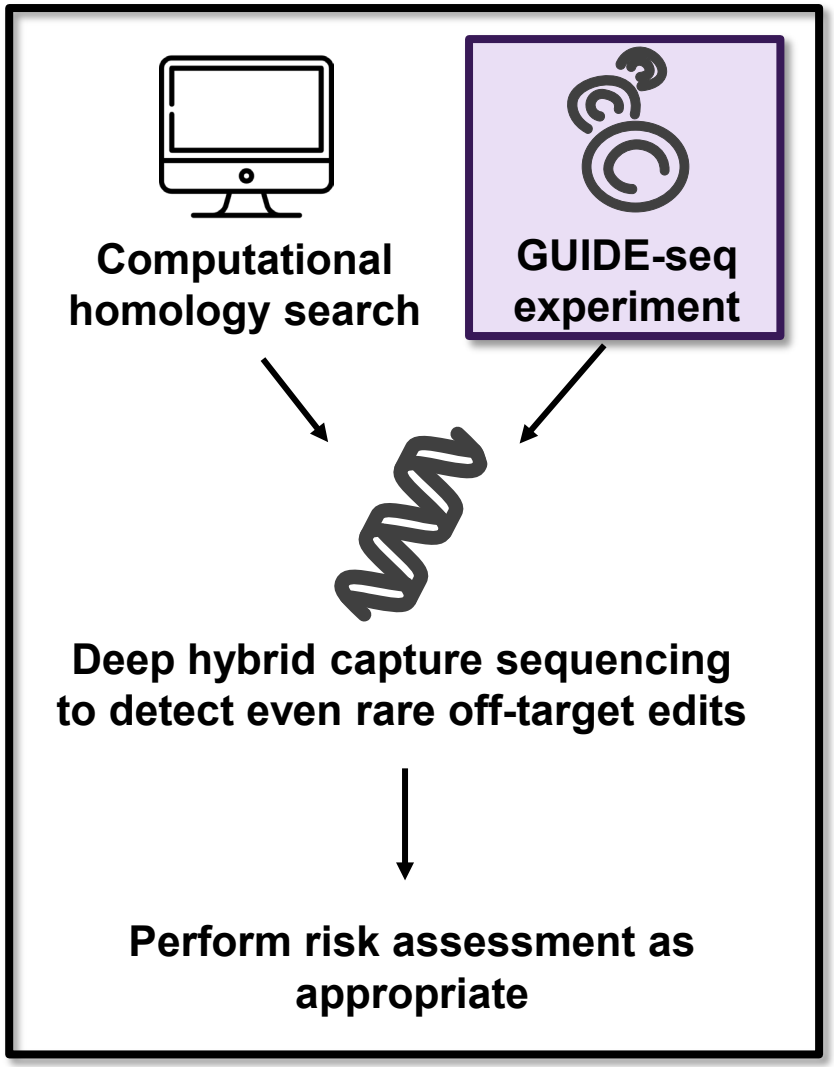
1: Stemmer et al. 2015; 2: Haeussler et al. 2016; 3: Cradick et al. 2015

Background: Probability of Off-Target Editing is Low at Sites with Greater Than 3 Mismatches to gRNA

Mismatches	Per-site probability of editing (%)
1	58%
2	13%
3	1.6%
4	0.06%
5	0.005%
6	0.0002%

Data adapted from Figure 1 in Haeussler et al. 2016; estimates primarily based on sites with NGG PAM and no bulges.

Nomination: Empirical GUIDE-seq Experiment



GUIDE-seq is a well-established laboratory method to nominate candidate off-target sites

- Performed directly in **human CD34+** cells, the relevant cell type, physiology and chromatin structure
- Performed in **patient samples with SCD** and TDT

GUIDE-seq is **highly sensitive** for true edits

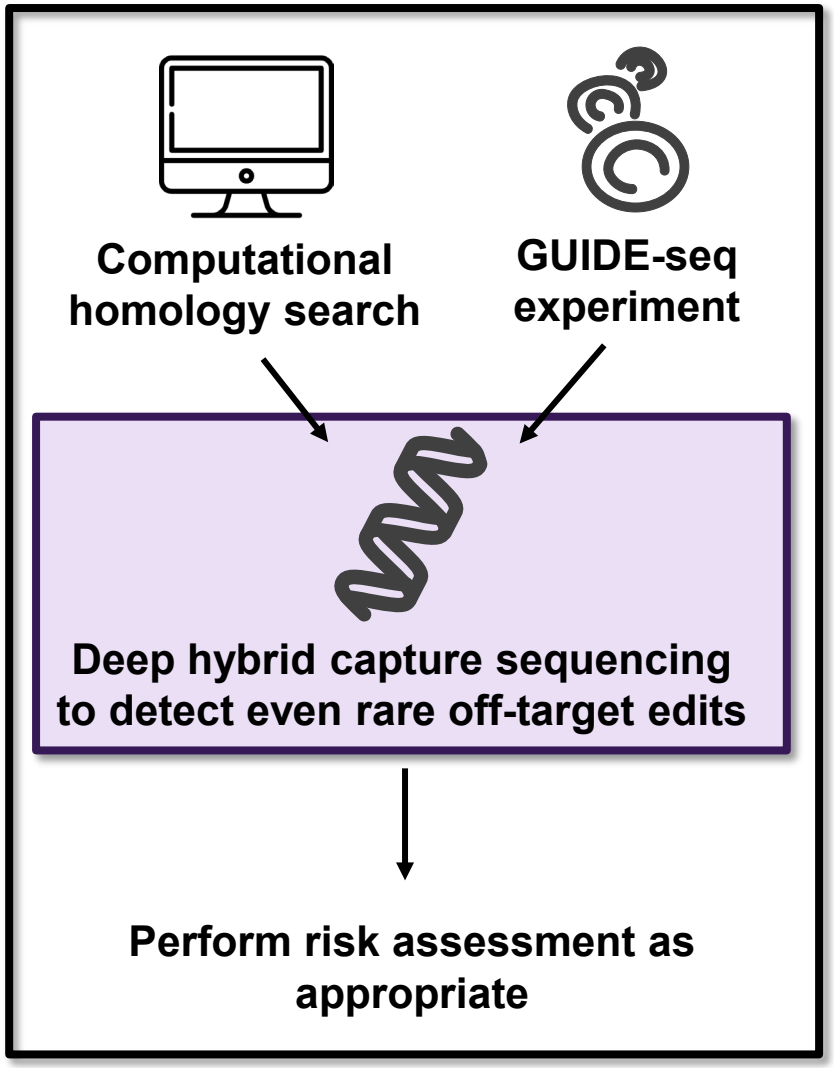
- On-target site served as **internal positive control**

GUIDE-seq also has a **high rate of false-positives**

- Due to naturally occurring double-strand breaks

Tsai et al. 2015; Chaudhari et al. 2020

Testing: Hybrid Capture Sequencing



Sites nominated by homology search and by GUIDE-seq were each tested using high-coverage hybrid capture sequencing in both edited and unedited cells

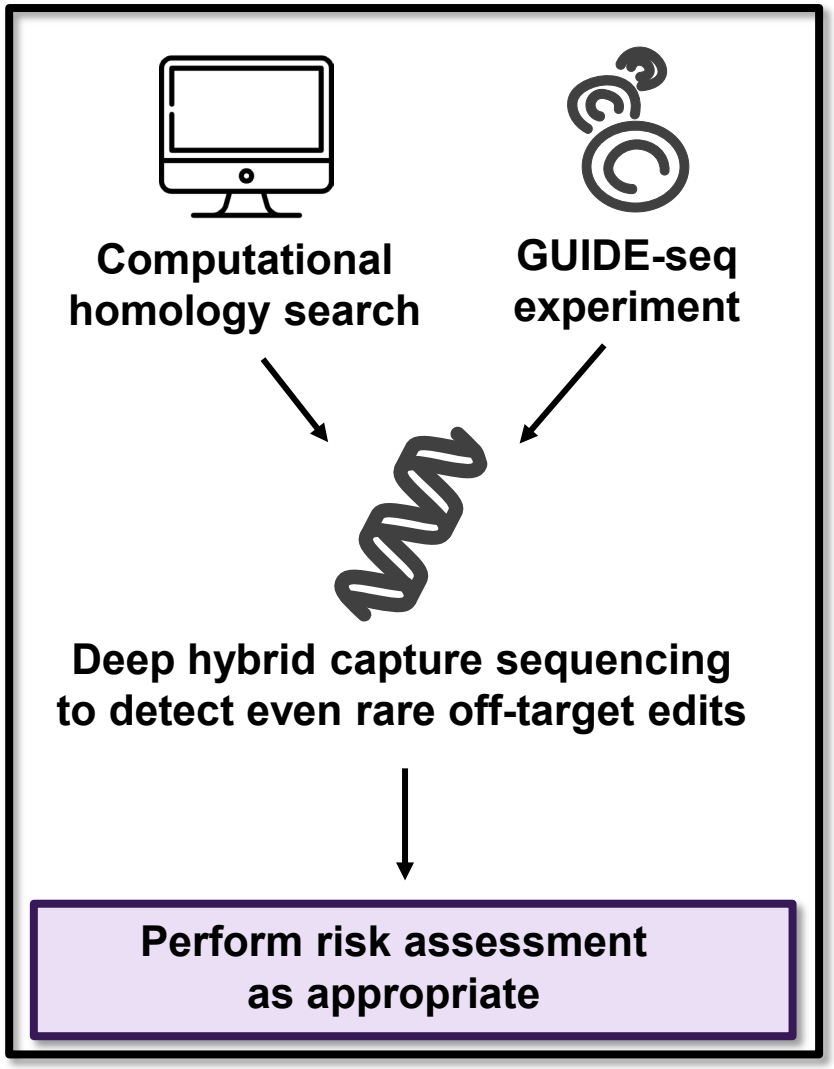
To **maximize sensitivity**, sequenced each site to high depth

- Provides sensitivity to detect off-target editing of ≥0.2%
- Both **specific and accurate** for edits at nominated sites

As in GUIDE-seq, in each hybrid capture study the on-target *BCL11A* site served as an **internal positive control**

- **Confirms** editing occurred and could be detected

Framework: Risk Assessment



We performed a **risk assessment** of any sites meeting either of two criteria:

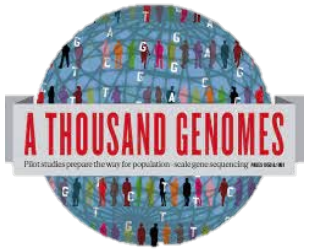
1. Sites confirmed to have off-target edits (none observed)
2. Candidate sites nominated based on genetic variation for which the rare allele is not present in tested samples

Key questions considered in risk assessment:

- Does the off-target site overlap a gene known to play a role in hematological malignancy?
- Does the off-target site overlap an exon?
- Does the off-target site overlap a gene known to play a functional role and be expressed in blood cells?

Inclusion of genetic diversity

Inclusion of Genetic Diversity Into Off-Target Analysis



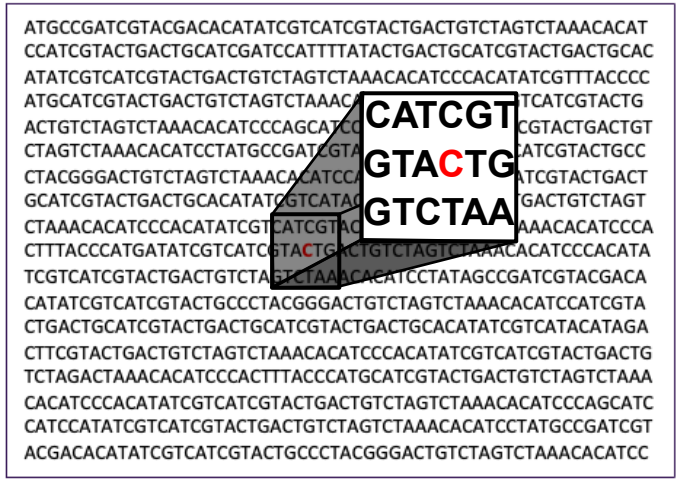
Performed a **variant-aware homology search** incorporating knowledge of human genome sequence diversity

- Included all sites in the 1000 Genomes Project database with a **frequency > 1%** in any continental group
- 1000 Genomes Project continental groups: residing in or with ancestry from **Africa**, East Asia, South Asia, Europe and the Americas
- Nominated **50 additional candidate off-target sites**

Hybrid capture sequencing in **14 individuals of diverse ancestry** including 4 African American donors of whom 3 have Sickle Cell Disease

Background: Most Human Genetic Variation is Common, Shared, and Occurs Outside of Protein Coding Exons

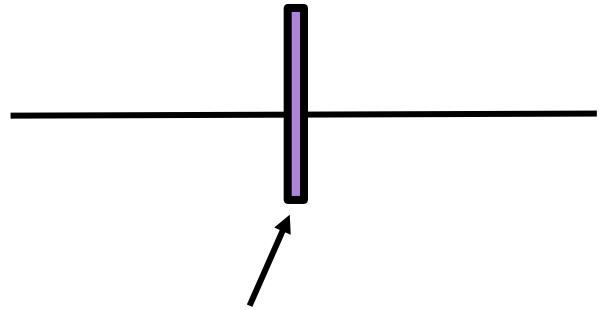
Any two human genome sequences differ at only 0.1% of DNA letters[1,2,3]



Of those that vary, ~90% are common and shared across populations[3]

Because most human genetic variation is common and shared, it is possible to build a comprehensive database

Most variants (99%) occur outside of coding regions



Coding exons are ~1% of human genome[4]

Most human genetic variation has no functional impact

1. Jorde et al. 2004; 2. The International HapMap Consortium 2003; 3. 1000 Genomes Project Consortium 2015; 4. The ENCODE Project Consortium 2013

Background: 1000 Genomes Project is an NIH-Funded, Global Reference Database of Human Genetic Variation

The 1000 Genomes Project collected and performed whole genome sequencing of **2,504 individuals** from **26 populations**

- 5 continental groups**:** Africa, East Asia, South Asia, Europe and the Americas

Sample set includes N=661 individuals residing in or with recent ancestry from Africa

Samples residing in or with recent African ancestry	Number of individuals
Esan in Nigeria	99
Gambian in Western Division, Mandinka	113
Luhya in Webuye, Kenya	99
Mende in Sierra Leone	85
Yoruba in Ibadan, Nigeria	108
African Caribbean in Barbados	96
People with African Ancestry in Southwest USA	61
Total	**661**

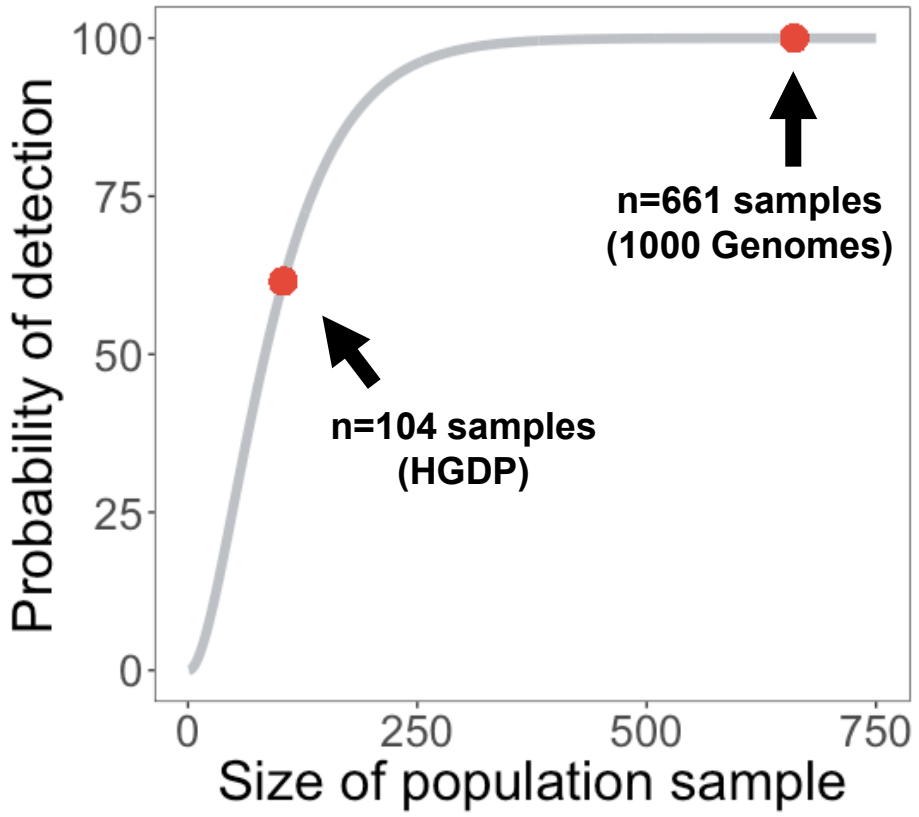
1000 Genomes Project Consortium 2015

Comparison: The 1000 Genomes Project and the Human Genome Diversity Project

Criterion	1000 Genomes	HGDP
Informed consent and community consultation for public release of samples and data	Yes	No
Number of individuals	2,504	929
Number of individuals with ancestry from sub-Saharan African	661	104
Number of individuals residing in sub-Saharan Africa	504	104
Number of individuals residing in USA with African ancestry	61	0
Number of total variants	83 million	76 million

The 1000 Genomes Project database is an appropriate resource for studies of human genome sequence variation relevant to the exa-cel target population

Sample Size of 1000 Genomes Project is Well Powered To Discover Variants with >1% Frequency



Probability of seeing a variant with true frequency 1% in at least two individuals

- **Power calculation**: sample size of the 1000 Genomes Project of n=661 individuals residing in or with recent African ancestry is sufficient to discover variants with frequency >1%
- **Validation**: internal[1] and external[2] evaluations document completeness of 1000 Genomes Project database to detect variants with > 1% frequency

1. 1000 Genomes Project Consortium 2015; 2. Byrska-Bishop et al. 2022

Results

Summary: Three Off-Target Studies Did Not Detect Any Evidence for Off-Target Editing

Healthy Donor Study #1 (n=4)

Broad homology search up to 5 mismatches

>2,500-fold median sequence depth

↓

No off-target editing detected

Healthy Donor Study #2 (n=4)

Focused homology search up to 3 mismatches

>15,000-fold median sequence depth

↓

No off-target editing detected

SCD and TDT Study #3 (n=6*)

Focused homology search incorporating genetic diversity

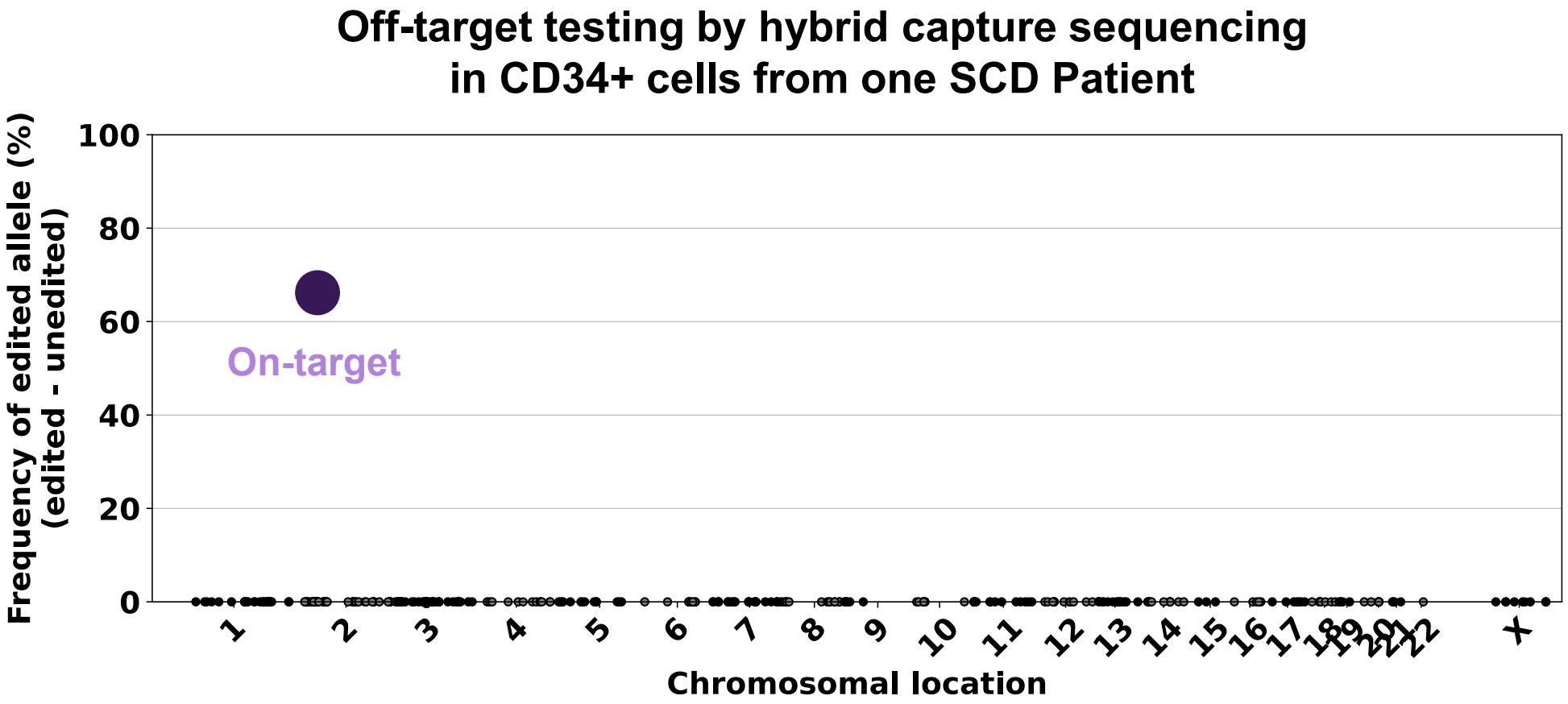
>19,000-fold median sequence depth

↓

No off-target editing detected

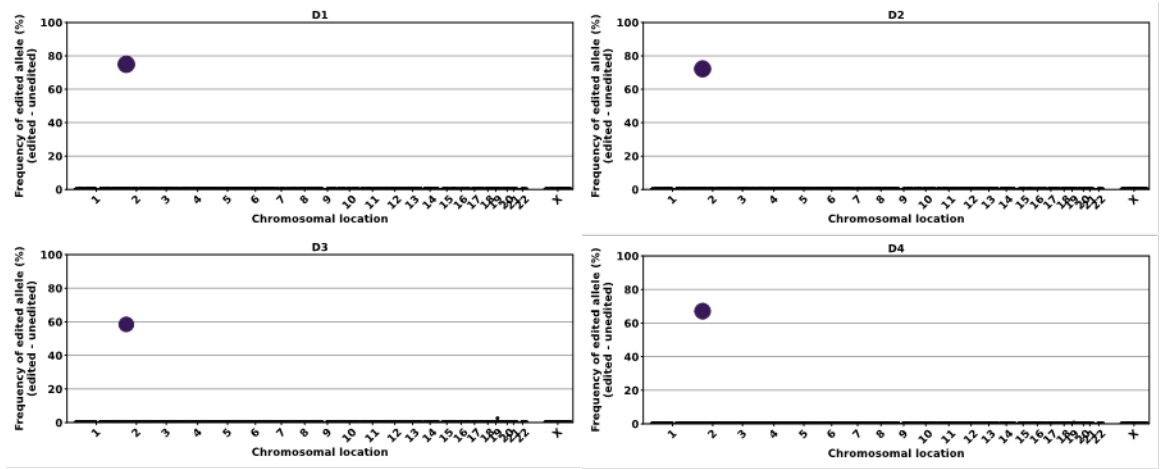
*Candidate sites with frequency ≤ 10% were tested in 3 patient samples

Results: Hybrid Capture Sequencing in CD34+ Cells From a Patient with SCD at On-Target and Candidate Off-Target Sites

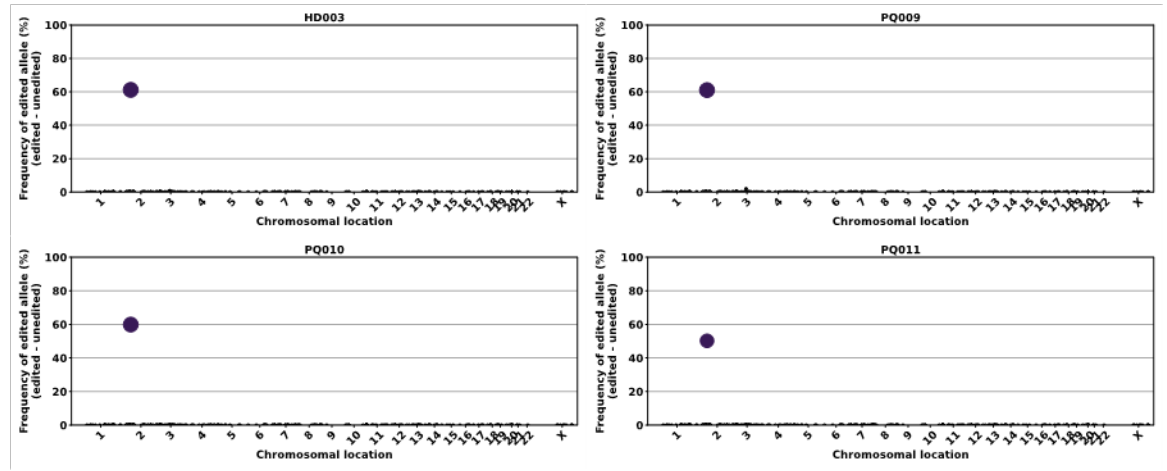


Results: Hybrid Capture Sequencing in CD34+ Cells From Healthy Donors at On-Target and Candidate Off-Target Sites

Healthy Donor Study #1 (n=4)



Healthy Donor Study #2 (n=4)

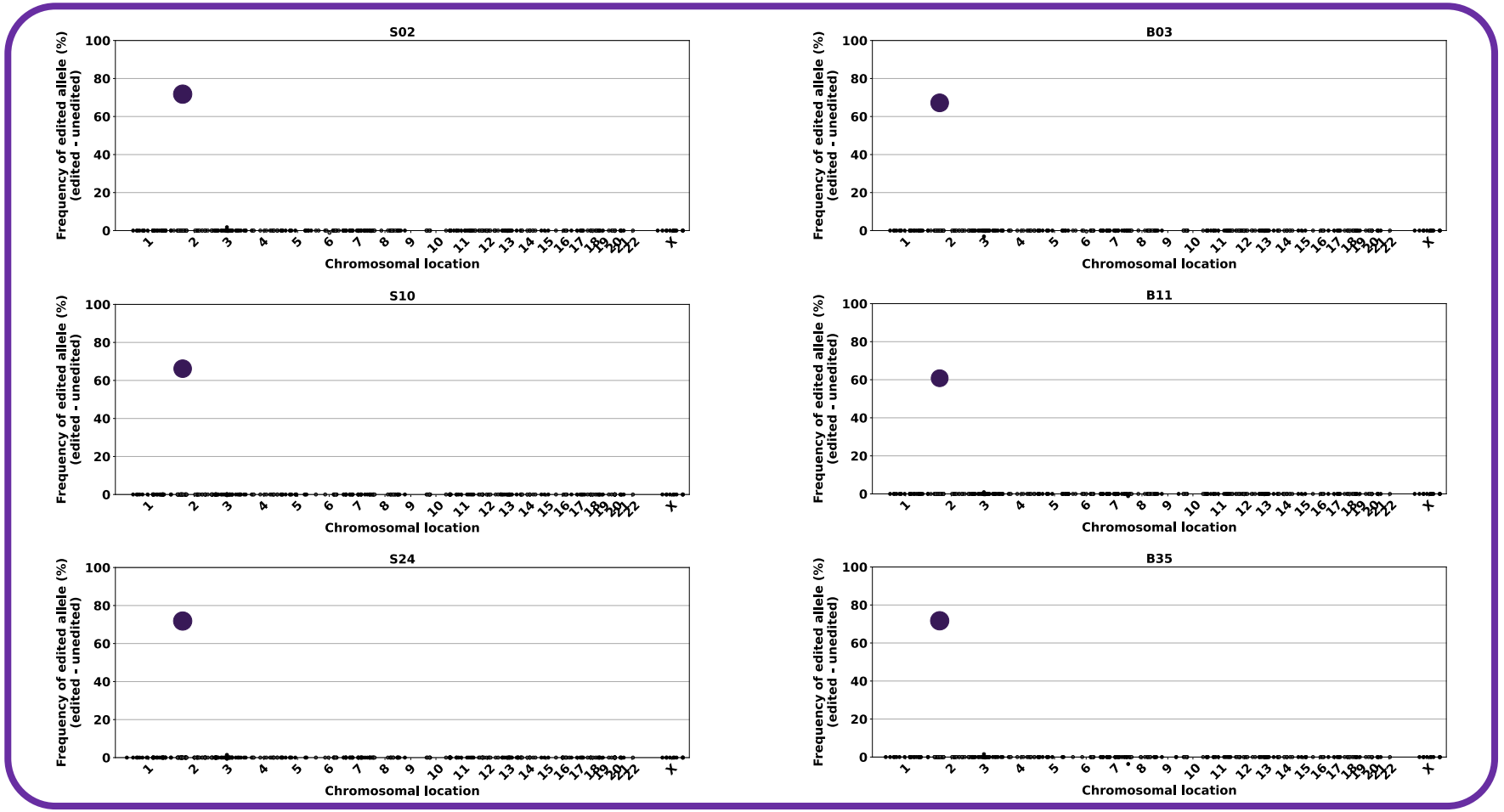


chr19 contains a false positive homopolymer site[1] with comparable levels of indels observed in both unedited and edited samples

1. Ross et al. 2013

Results: Hybrid Capture Sequencing in CD34+ Cells From SCD Patients at On-Target and Candidate Off-Target Sites

SCD and TDT
Study #3 (n=6)



chr3 centromere contains a false positive hotspot for naturally-occurring double-strand breaks[1] that is observed in both unedited and edited cells

1. Tsai et al. 2015

Analysis of Candidate Sites Nominated by Sequence Diversity

- We used the hybrid capture sequencing data to identify the genotype of each patient sample at each of the 50 sites nominated by genetic variation

- At **9 of 9 candidate sites** where genetic variant had **global frequency > 10%,** one or more donor samples carried the low frequency allele
  - Of low frequency variants (global frequency <10%, frequency >1% in any continental population), **3/41** were present in one or more samples

- Risk assessment of all sites from variant-aware search identified no overlap with genes implicated in hematological malignancy (MyeloSeq™)
  - All are non-coding and do not overlap with exons at any human gene

MyeloSeq™, Washington University Pathology Services, St. Louis MO

Analysis of Candidate Off-Target Site Described in Publication by Cancellieri et al. (2023)

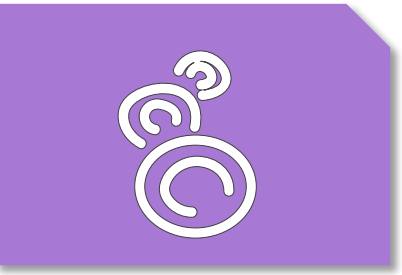
- Cancellieri et al. described a computational algorithm for identifying candidate off-target sites based on genetic diversity, and used *BCL11A* as a test case[1]
  - Highlighted a variant site as having potential for off-target editing

- Our initial exa-cel homology search identified the Cancellieri et al. site (based on alternative PAM), and the site was evaluated in all 3 off-target assessments
  - No off-target editing was found at this site in any individual
  - Genotyping: none of the 14 donors carried the low frequency allele

- Risk assessment of Cancellieri et al. site did not identify exa-cel specific risk
  - No known or hypothesized role in myeloid malignancy
  - Non-coding intron in the *CPS1* gene — not expressed in blood cells[2]

1. Cancellieri et al. 2023; 2. Fagerberg et al. 2014

Conclusion: Comprehensive Evaluation Did Not Identify Evidence of Off-Target Editing by Exa-Cel



Exa-cel was designed to minimize risk due to off-target editing

Extensive empirical assessment observed no off-target editing across three studies

No off-target editing observed at candidate sites nominated based on genetic diversity, and risk assessments did not identify exa-cel specific risk

Comprehensive non-clinical package did not identify exa-cel specific risk

Clinical Safety

Christopher Simard, MD

Vice President, Global Patient Safety

Vertex Pharmaceuticals

Summary of Key Clinical Safety Results

Adverse Events	AEs and SAEs after exa-cel consistent with myeloablative conditioning with busulfan and HSCT
Engraftment	No graft rejection or graft failure 100% achieved neutrophil and platelet engraftment
Sub-groups	Consistent safety profile among adults and adolescents
Long-term Safety	No new or unique safety events in Study 131 including no malignancies
Pharmacovigilance Plans	Product labeling, Long-term follow-up study 131 and post-approval registry-based study

Safety Database Supports Benefit-Risk Assessment for Adult and Adolescent Patients With Severe SCD

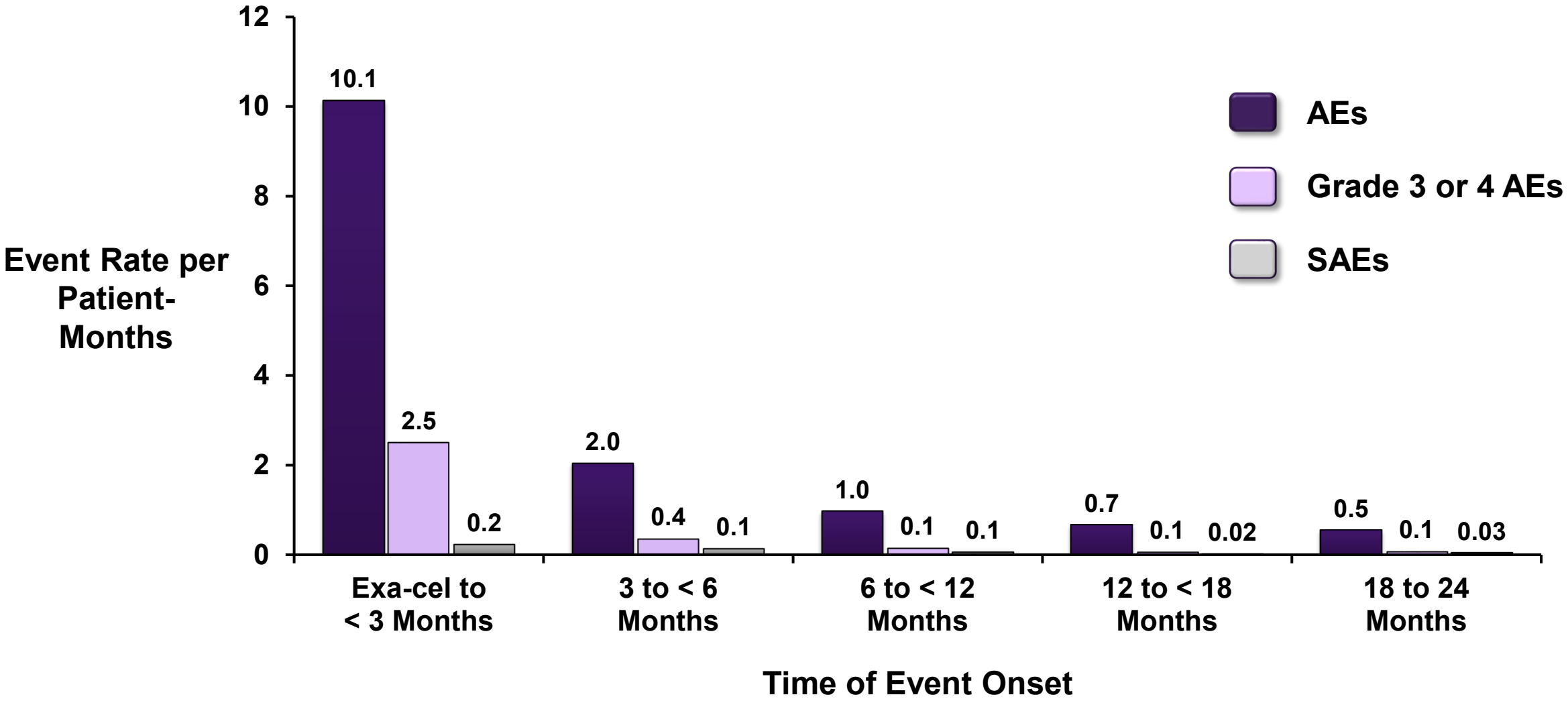
	SCD Study 121 + Study 131
Number of patients dosed	**44**
Follow-up duration, months Mean (min, max)	**20.1 (0.8, 48.1)**
Patient-years of safety follow-up, total	**73.5**
Patients with ≥ 18 Months	**30 (68%)**

Exa-cel Adverse Event Profile Consistent With Myeloablative Conditioning and HSCT

	Study 121 Patients N = 44	Number of Adverse Events
AEs	100%	1948
Related or possibly related to exa-cel	30%	25
Related or possibly related to busulfan	100%	661
Grade 3 or 4	95%	415
SAEs	45%	66
Related or possibly related to exa-cel	0	0
AEs leading to death	2%	1
New malignancies	0	0

Study 121 FAS after exa-cel infusion through Month 24

AEs Occurred Mostly Within First 3 Months Rate Decreased Over Time



Study 121 FAS after exa-cel infusion through Month 24

Most Common Adverse Events After Exa-cel

Preferred Term	Study 121 N = 44	
	Any AE (≥ 40%)	AEs Grade ≥ 3
Nausea	70%	9%
Stomatitis	64%	55%
Vomiting	57%	5%
Febrile neutropenia	55%	48%
Abdominal pain	50%	11%
Headache	50%	9%
Pruritus	50%	11%
Decreased appetite	48%	41%
Platelet count decreased	48%	48%
Constipation	45%	9%
Pain in extremity	45%	5%
Arthralgia	43%	7%
Pyrexia	41%	0

Study 121 FAS after exa-cel infusion through Month 24

All Patients Achieved Neutrophil and Platelet Engraftment After Exa-cel Infusion

	Neutrophil Engraftment N = 44	Platelet Engraftment N = 44
Patients who achieved engraftment, n (%)	**44 (100%)**	**44* (100%)**
Time to engraftment (days)		
Median	**27**	**35**
Min, max	**15, 40**	**23, 126**

***Includes one patient achieving platelet engraftment after the data-cut for the submission (Day 26)**
Study 121 FAS after exa-cel infusion through Month 24

Pharmacovigilance Plans to Continue to Monitor the Safety of Exa-cel Long-Term to Ensure Continued Favorable Benefit-Risk

Pharmacovigilance Plan Summary

- Product labeling
  - Exa-cel-specific risk of delayed platelet engraftment
  - Risks with busulfan myeloablative conditioning used with the exa-cel regimen

- Monitoring for any long-term effects, including potential malignancy
  - Continuation of 15-year, long-term follow-up clinical study (131)
  - Post-approval: initiation of a registry-based study to follow patients treated with exa-cel for 15 years

Multiple Surveillance Mechanisms in Place to Assess Long-Term Safety Post-Approval

	Ongoing Vertex Long-term Follow-up Clinical Study (Study 131)	CIBMTR Registry Routine Data Collection (100% Allo-HSCT and ~85% Auto-HSCT in US)[1]		Planned Vertex Registry-based Study
		Essential data	Comprehensive data	
Patient Population	All patients treated with exa-cel in clinical studies (N=101)[2]	Total > 1,500 SCD[3]	Subset > 700 SCD[3]	250 patients with SCD treated with exa-cel[4]
Follow-up duration	15 years	Lifetime		15 years
SAEs (including malignancy) reported to Vertex within 24 hours	All	-	-	All
Neutrophil and Platelet Engraftment	✓	✓	✓	✓
Malignancy	✓	✓	✓	✓
Mortality	✓	✓	✓	✓
CBC[5]	✓	-	✓	✓
Effectiveness (e.g. HbF, VOCs)	✓	-	✓	✓
Hemolysis markers	✓	-	✓	✓
Non-malignant hematologic disorders	✓	-	-	✓
Sample storage (DNA)	Bone marrow[6]; Blood	-	-	-

CBC: complete blood count; CIBMTR: Center for International Blood and Marrow Transplant Research

1. Data can be accessed for research purposes for consenting patients; All planned exa-cel treatment centers in the US participate in and report data to CIBMTR.
2. N reflects patients projected for enrollment after treatment with exa-cel in pivotal SCD (N=45; 1 patient died in study 121 and cannot enroll in study 131) and transfusion-dependent β-thalassemia (TDT) (N=56) studies.
3. Number of transplants since 1991 (Source: CIBMTR Cure Sickle Cell Initiative; Last updated: February 10, 2023).
4. From CIBMTR and European Bone Marrow Transplant (EBMT) registries.
5. CBC with differential in Study 131; CBC and select differential results in CIBMTR Registry and Vertex Registry-based study.
6. Bone marrow available: Baseline, Months 6, 12, and 24 (SCD and TDT), and Months 36, 48, and 60 (TDT); Months 48 and 60 (TDT) are conditional.

Conclusion: Exa-cel Safety Profile is Well-Characterized, Safe and Well-Tolerated in Patients With Severe SCD

- Clinical safety profile consistent with busulfan myeloablation and HSCT
- Delayed time to platelet engraftment is the only exa-cel specific risk
- All patients achieved neutrophil and platelet engraftment
- Consistent safety profile between adults and adolescents
- No long-term safety findings from patients in long-term follow-up
- Long-term monitoring of safety will continue post-approval

Exa-cel demonstrates favorable safety and tolerability profile in adult and adolescent patients with severe SCD

Clinical Perspective

Haydar Frangoul, MD

Medical Director Pediatric Hematology/Oncology and Cellular Therapy
Sarah Cannon Research Institute

Sickle Cell Disease is Debilitating and Life-Shortening With High Unmet Need

- Debilitating pain and chronic, progressive complications across multiple organs
- Diminished quality of life for patients and families
  - Significant morbidity
- Median age of death = 45 years[1]
- Patients need another curative therapy option beyond allo-HSCT
  - 80-85% of patients with SCD do not have a suitable donor
  - Risks associated with transplant that a patient must consider

1. Lee et al. 2019

Impact of Exa-cel on Patients' Lives

Patient 1

- 33-year-old female
- 3.5 hospitalizations annually
- Severe and painful SCD crises: inability to walk and feed herself
- Inability to keep a job due to pain
- Struggling to care for family

Exa-cel

- **VOC-free**
- Working full-time
- Spending time with family

Patient 2

- 13-year-old female
- SCD diagnosis on newborn screening
- First hospitalization at 6 months of age, and hospitalized many times annually (despite hydroxyurea)
- Inability to regularly attend school

Exa-cel

- **VOC-free**
- Attending school and enjoying teenage years

Exa-cel Offers Autologous Treatment Option That Functionally Cures SCD

Avoid allogeneic HSCT risks

- Acute and chronic graft-versus-host disease
- Graft rejection
- Need for immunosuppressive therapies

Receive transformational benefit

- Freedom from severe painful VOCs
- Ability to return to school, work, and normal activities

Treating SCD Early is Important Before End-Organ Damage Accumulates

- SCD-accumulated damage prior to HSCT is irreversible
- Transplant can prevent future damage but will not eliminate previous injury
- Patient trajectory varies but SCD generally worsens with age
- Exa-cel data consistent in adolescents and adults
  - Same mechanism of sickle cell disease
  - Same mechanism of action
  - Myeloablative conditioning and transplantation procedures often tolerated in adolescents better than adults

Exa-cel Studies Demonstrated Positive Benefit-Risk

- Transformational and durable clinical benefit
- Patients received substantial clinical benefit which was consistent in adults and adolescents
- Generally safe and well-tolerated
- Safety profile consistent with busulfan myeloablation and HSCT and manageable

Approval of exa-cel would provide life-changing treatment for patients suffering with sickle cell disease

Exa-cel for the Treatment of Sickle Cell Disease (SCD) in Patients ≥ 12 Years With Recurrent Vaso-Occlusive Crises (VOCs)

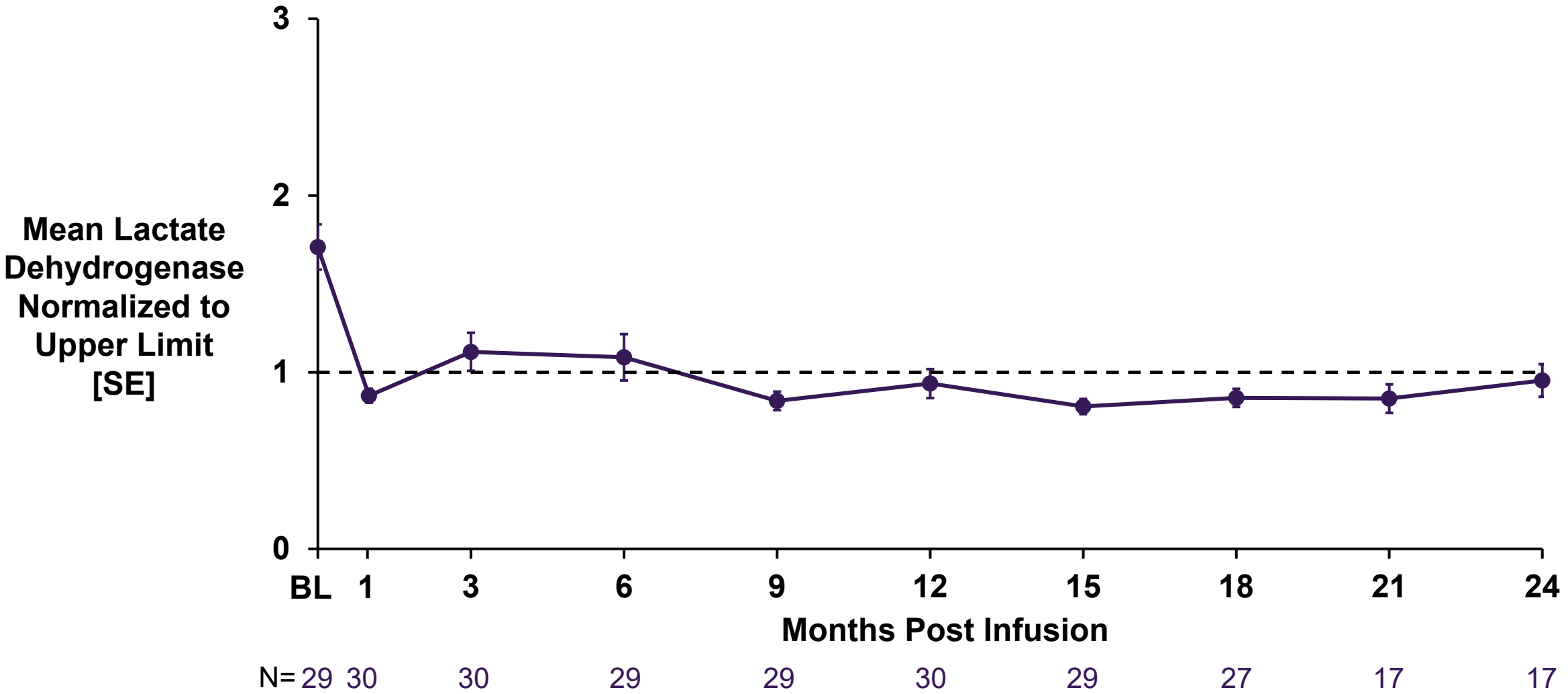
October 31, 2023

Cellular, Tissue, and Gene Therapies Advisory Committee

Vertex Pharmaceuticals

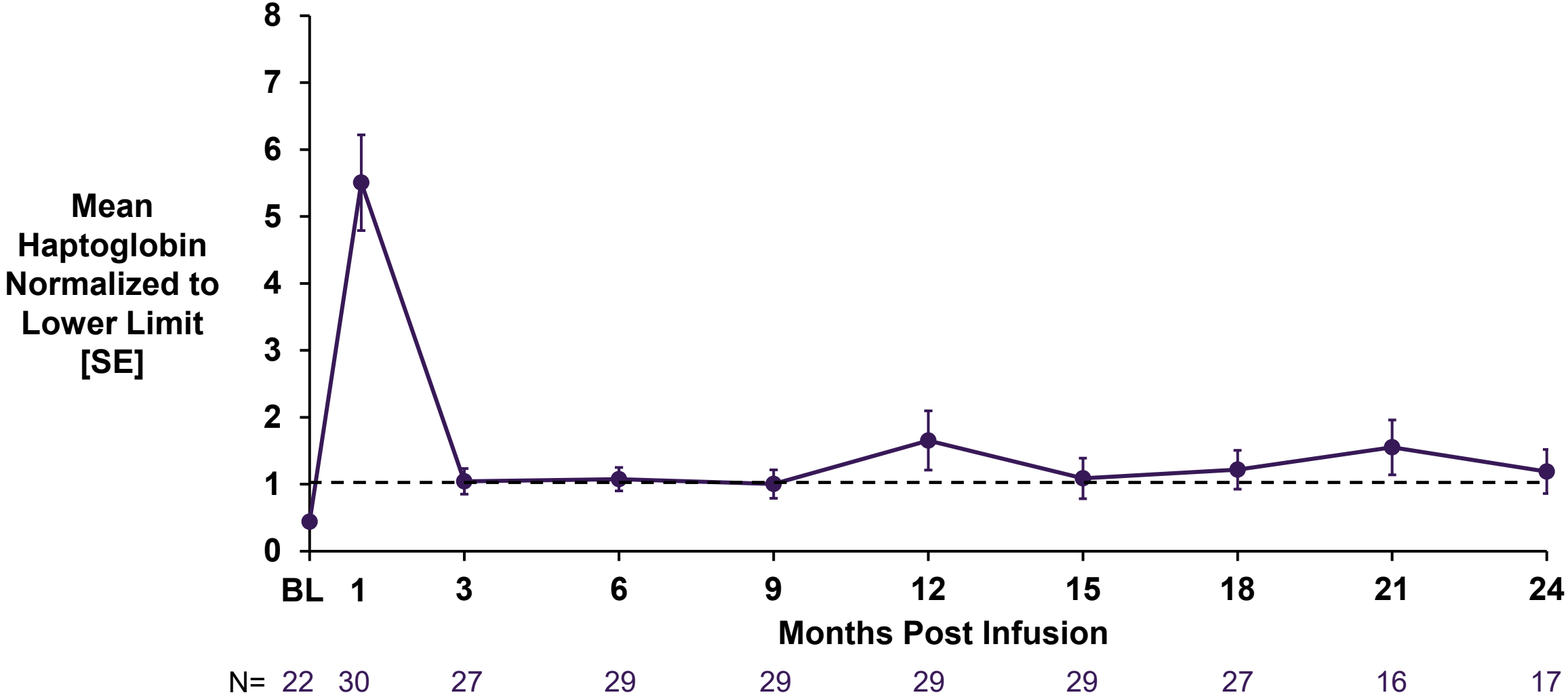
Mean Lactate Dehydrogenase Levels Normalized After Exa-cel

SF-101



BL: baseline

Haptoglobin Is Detectable in All Patients, Levels Generally Normalized After Exa-cel



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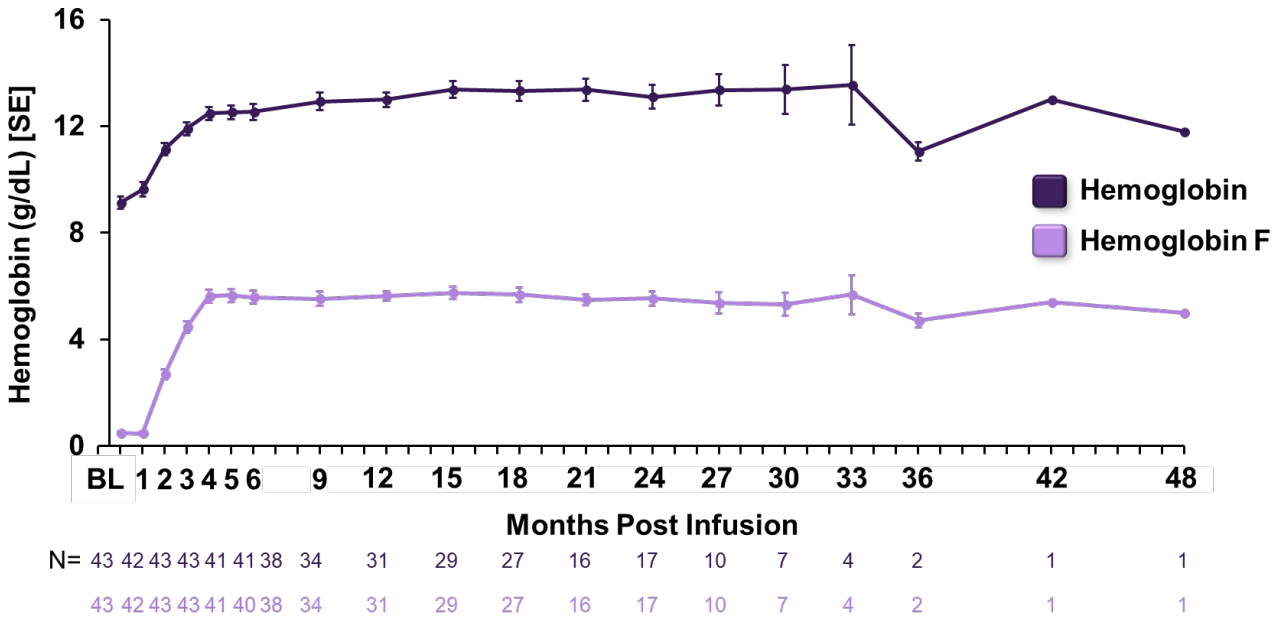
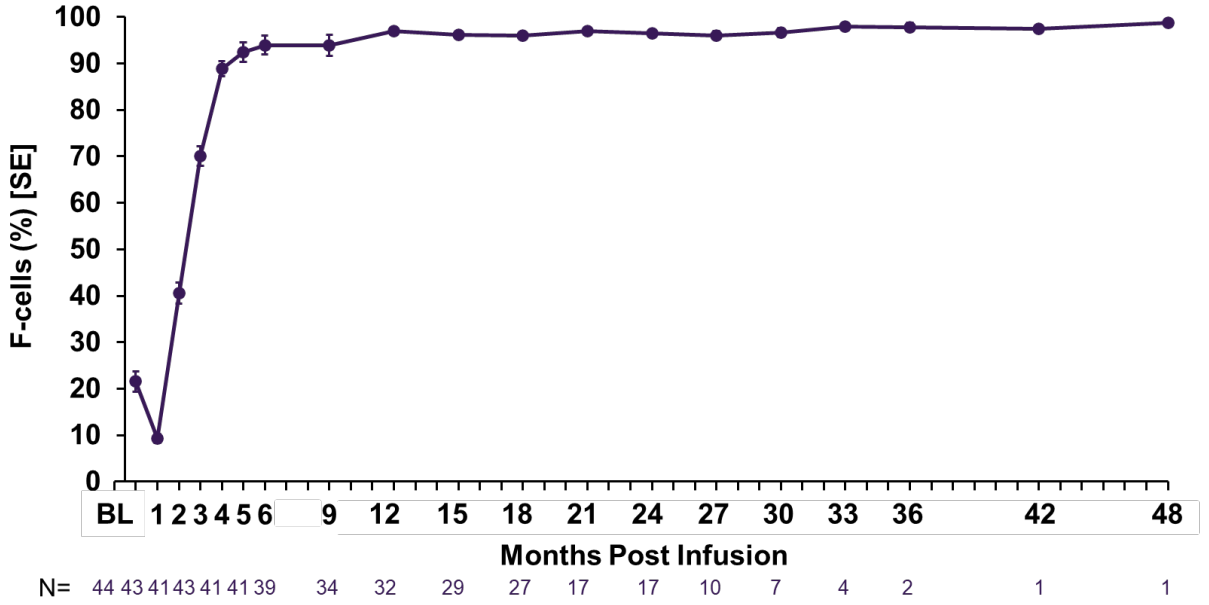
Exa-cel Achieved Rapid, Robust, and Durable Levels of Total Hemoglobin and Hemoglobin F in a Pancellular Distribution

Increases in Hemoglobin and Hemoglobin F



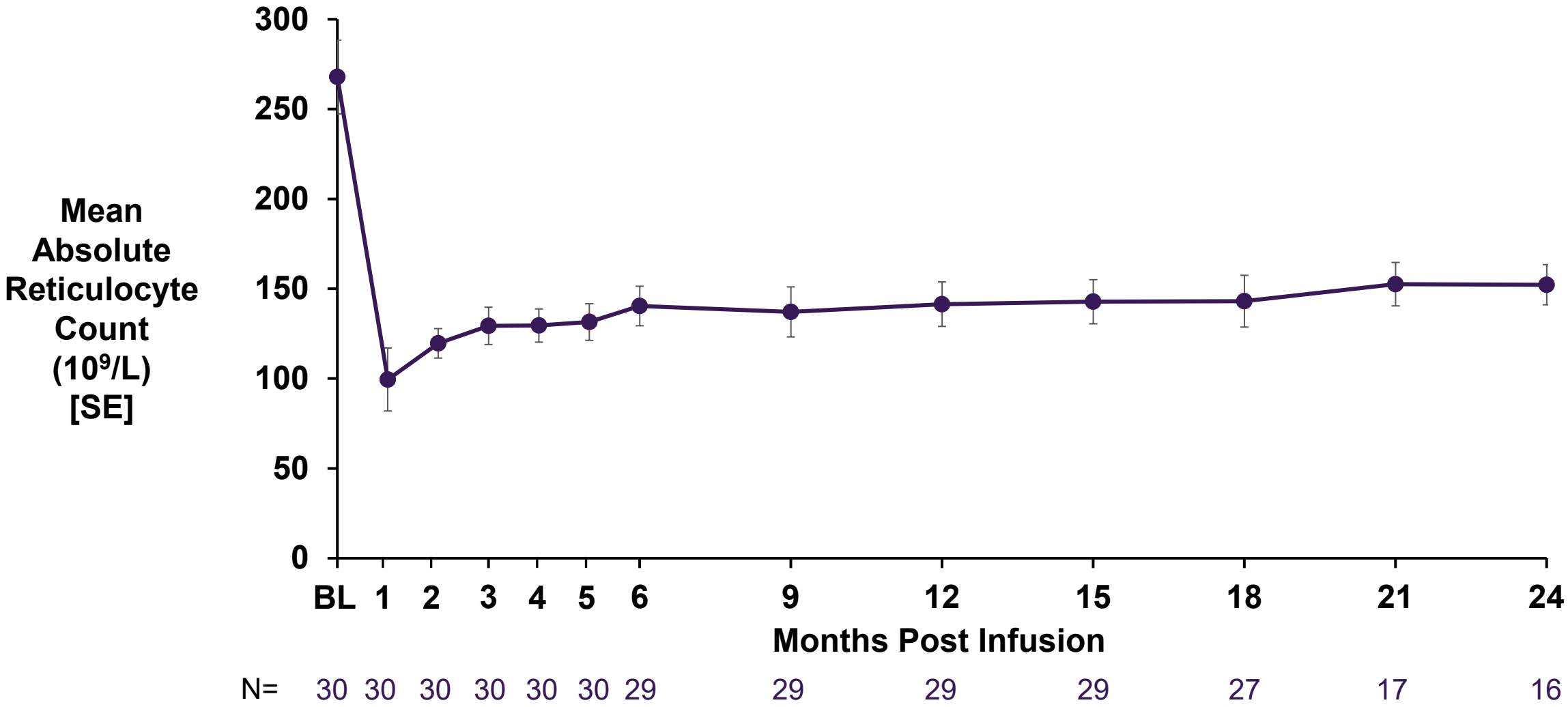
Pancellular Distribution of HbF



BL: baseline

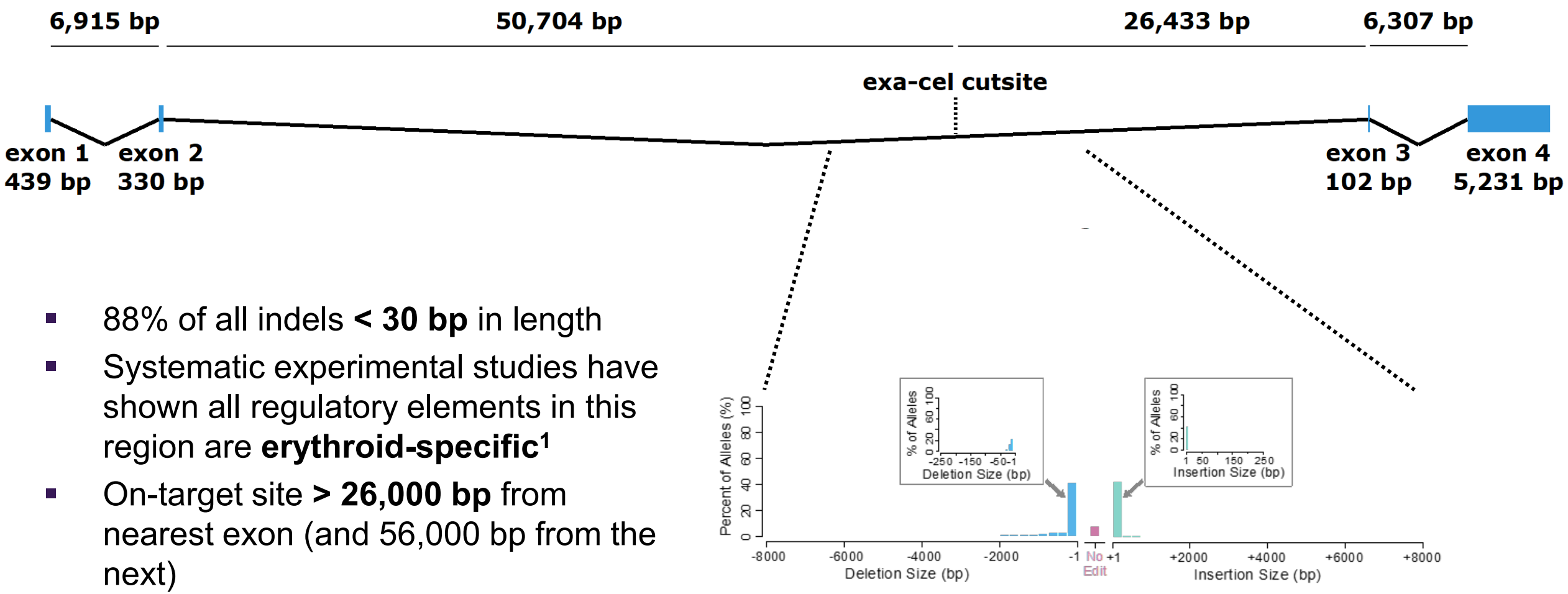
FAS

Absolute Reticulocyte Counts Improve After Exa-cel



BL: baseline

On-Target Editing: Limited to the *BCL11A* Erythroid-Specific Enhancer



- 88% of all indels **< 30 bp** in length
- Systematic experimental studies have shown all regulatory elements in this region are **erythroid-specific**[1]
- On-target site **> 26,000 bp** from nearest exon (and 56,000 bp from the next)

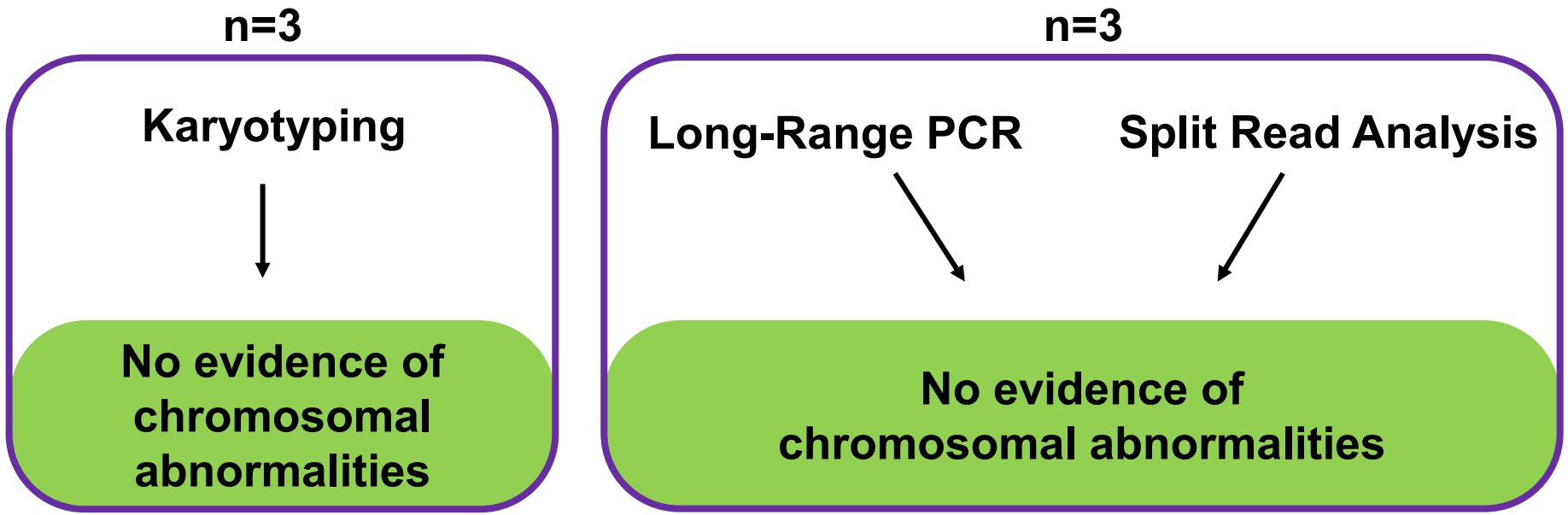
1. Bauer et al 2013; Canver et al 2015; Smith et al 2016

Rationale for Ongoing Clinical Monitoring

- Clinical study demonstrates strongly positive benefit/risk
- Comprehensive nonclinical package: no identified off-target events
- Risk assessment of rare variants performed
- Rigorous clinical and laboratory follow-up is needed
- Approach in clinical study and pharmacovigilance plan to assess potential risk is close clinical monitoring

Exa-cel has highly positive benefit/risk for treatment of SCD patients who have severe disease, high unmet need and lack of available treatment options

No Chromosomal Abnormalities Identified in Exa-cel



Additional factors that inform potential risk of chromosomal abnormalities:

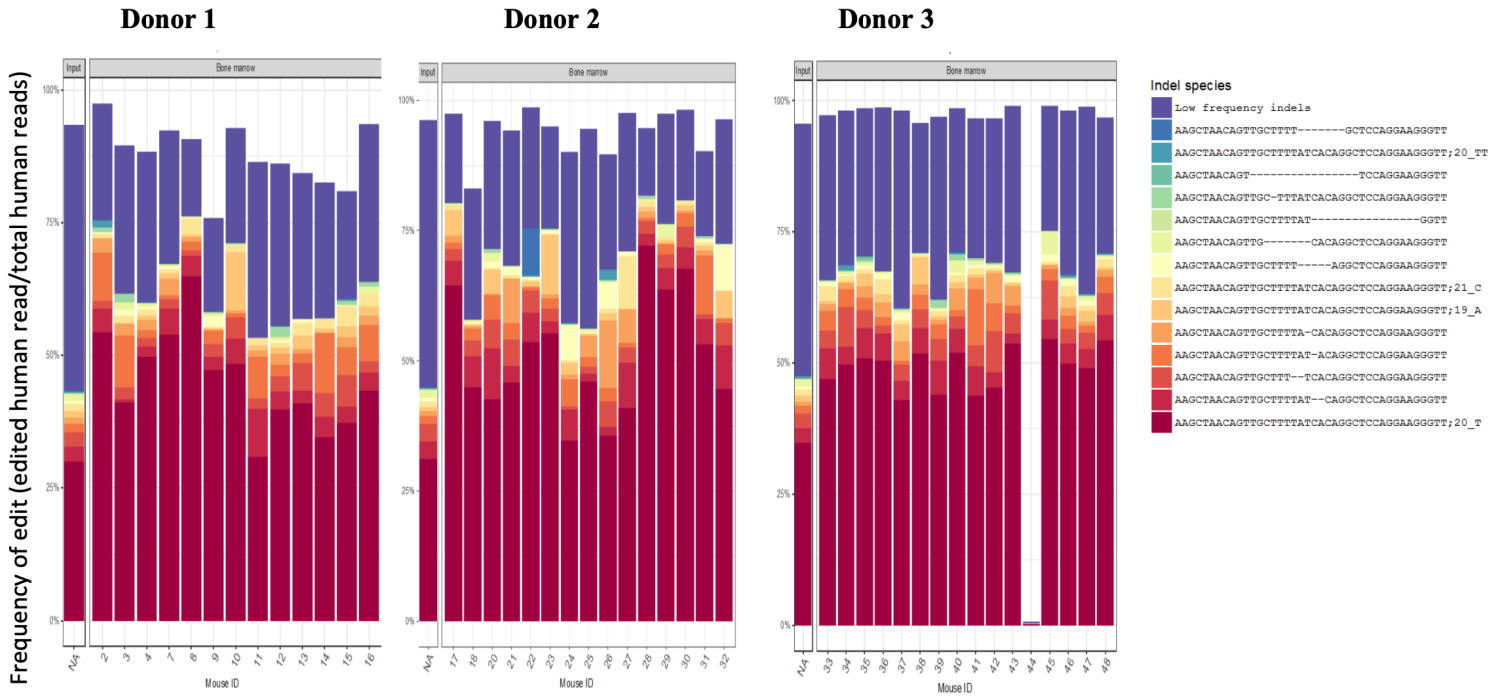
- Creation of a translocation requires editing at two sites in genome, and the non-clinical package did not identify sites with off-target editing with exa-cel
- Cellular DNA repair mechanisms identify DNA damage and repair it, or induce apoptosis
- To impact the patient, cell with a chromosomal abnormality would need to survive and engraft

Ongoing Assessment of Benefit and Risk

- Totality of non-clinical and clinical trial data demonstrate a **compelling benefit-risk profile** for patients with **severe sickle cell disease**
- Gene editing is a rapidly evolving field, and **ongoing collection** of clinical data and samples can support analysis as new information emerges
- The ongoing **CLIMB-131** study is following all patients from the pivotal program for **15 years** (n=45 people with SCD and n=45 with TDT)
- **Pharmacovigilance** program is still being finalized with FDA: proposal is for 250 individuals followed with clinical monitoring

Analysis: Indel Patterns Across Different Donors

Non-Clinical Animal Studies



Manufacturing Process Qualification

- 19 lots tested
- Indel patterns assessed
- Consistent with non-clinical data

Frangoul et al. 2021