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EXAGAMGLOGENE AUTOTEMCEL (EXA-CEL) FOR THE TREATMENT OF SICKLE CELL DISEASE IN PATIENTS 12 YEARS AND OLDER WITH RECURRENT VASO-OCCLUSIVE CRISES

BLA125787

SPONSOR BRIEFING DOCUMENT

CELLULAR, TISSUE AND GENE THERAPIES ADVISORY COMMITTEE

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Abbreviation	Definition
ACS	acute chest syndrome
AE	adverse event
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALT	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement System
AUC	area under the concentration versus time curve
AVN	avascular necrosis
BCL11A	B-Cell Lymphoma/Leukemia 11A
BLA	Biologics License Application
BMTS	bone marrow transplantation subscale
bp	base pair
Cas9	CRISPR-associated 9 nuclease
cAUC	cumulative area under the concentration versus time curve
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
COVID-19	coronavirus disease 2019
CRISPR/Cas9	clustered regularly interspaced short palindromic repeats and CRISPR-associated 9 nuclease
CSSCD	Cooperative Study of Sickle Cell Disease
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLco	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
EAC	endpoint adjudication committee
eCTD	electronic common technical document
EES	Early Efficacy Set
EQ-5D-5L	EuroQol Questionnaire – 5 dimensions – 5 levels of severity
EQ-5D-Y	EuroQol Questionnaire – 5 dimensions – 5 levels of severity – youth version
EQ VAS	EuroQol Quality of Life Scale – Visual Analog Scale
exa-cel	exagamglogene autotemcel
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	Full Analysis Set
F-cells	circulating RBCs expressing detectable levels of HbF
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GVHD	graft-versus-host disease
Hb	hemoglobin

HbF	fetal hemoglobin
HbS	sickle hemoglobin
HF12	free from inpatient hospitalization for severe VOCs sustained for at least 12 months after exa-cel infusion
hHSPCs	human hematopoietic stem and progenitor cells
HLA	human leukocyte antigen
HPFH	hereditary persistence of fetal hemoglobin
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
HSPCs	hematopoietic stem and progenitor cells
HU	hydroxyurea
IA	interim analysis(es)
ICE	intermediate clinical endpoint
ICF	informed consent form
IFN	interferon
IND	Investigational New Drug (application) (US)
indels	insertions and deletions
INR	international normalized ratio
IV	intravenous
LDH	lactate dehydrogenase
LT-HSC	long-term hematopoietic stem cell
LVEF	left ventricular ejection fraction
Max	maximum
MCID	minimal clinically important difference
Min	minimum
MOA	mechanism of action
mRNA	messenger RNA
n	size of subsample
N	total sample size
NAT	nucleic acid test
NRS	numeric rating scale
NSAID	non-steroidal anti-inflammatory drugs
P	probability
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PedsQL	Pediatric Quality of Life Inventory
PES	Primary Efficacy Set
PK	pharmacokinetic, pharmacokinetics
PRO	patient-reported outcome
PT	Preferred Term
PV	pharmacovigilance
q6h	every 6 hours
qd	once daily
RBC	red blood cell

RMAT	Regenerative Medicine Advanced Therapy
RNA	ribonucleic acid
RNP	ribonucleoprotein
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SCD	sickle cell disease
SD	standard deviation
SE	standard error
TAMMV	time-averaged mean of the maximum velocity
TCD	transcranial Doppler
TDT	transfusion-dependent β-thalassemia
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
VF9	absence of any severe VOC (i.e., VOC free) for at least 9 consecutive months after exa-cel infusion
VF12	absence of any severe VOC (i.e., VOC free) for at least 12 consecutive months after exa-cel infusion
VOC	vaso-occlusive crisis

1 EXECUTIVE SUMMARY

1.1 Introduction

Exagamglogene autotemcel (exa-cel) is a one-time, single dose cellular product consisting of autologous CD34+ human hematopoietic stem and progenitor cells (hHSPCs) modified by CRISPR/Cas9-mediated gene editing that was developed to treat patients 12 years and older with severe sickle cell disease (SCD).

SCD is a serious, rare, debilitating, and life-shortening hemoglobinopathy (disorder of hemoglobin) with no broadly available curative options. SCD affects approximately 100,000 people in the US. Patients with severe SCD, as defined by recurrent vaso-occlusive crises (VOCs), are even more rare, estimated at 20,000 people in the US. In the US, approximately 90% of people with SCD are of African descent.[1] This demographic distribution contributes to SCD patients historically facing significant healthcare disparities which directly relate to the poor outcomes associated with SCD.[1] Overall SCD patient lifespan is shortened by 2 to 3 decades compared to the general population[2-6]; the median age at death is 45 years[1], with some patients only surviving to 20 years.[2-6] Patients with severe disease have even greater morbidity and mortality, including increased mortality in adults and adolescents.[2-4, 7-9]

All SCD patients share a common genetic cause and have the same underlying pathophysiology, regardless of age, sex, race, or disease genotype. SCD is caused by a single-nucleotide substitution which results in the amino acid valine replacing glutamic acid at position 6 of the β-globin chain, leading to sickle hemoglobin (HbS). In the deoxygenated state, HbS polymerizes, producing abnormal, sickle-shaped red blood cells (RBCs) with limited flexibility, increased adhesive and inflammatory properties, and a predisposition to hemolysis. These sickled RBCs trigger blockages in small- to medium-sized blood vessels, depriving downstream tissues of nutrients and oxygen, resulting in tissue infarction and ischemia/reperfusion injury. Clinically, these events manifest as severe, acute painful episodes (VOCs). These events not only require acute care at a health care facility but also culminate in progressive tissue damage in multiple end organs leading to their dysfunction and ultimately, failure. Hemolysis of RBCs leads to chronic anemia which also contributes to SCD morbidity, and poor quality of life, as well as contributing to mortality.[10-13] Patients who have severe disease are at even greater risk of these disease complications and have worse outcomes.[14]

There are no approved therapies developed specifically to prevent VOCs for patients with severe SCD; defined as 2 or more VOCs per year in each of the prior 2 years. Currently approved therapies require chronic use and include hydroxyurea (HU), voxelotor (Oxbryta®), and crizanlizumab (Adakveo®). HU has moderate efficacy in reducing but not eliminating VOCs[15], while voxelotor and crizanlizumab have not demonstrated a decrease in VOC rates.[16, 17]

As such, patients with severe SCD have a particularly high unmet need and allogenic hematopoietic stem cell transplant (allo-HSCT) is often considered. While holding curative potential, allo-HSCT has significant limitations and is not an option for the majority of patients with severe disease. Allo-HSCT requires a suitable stem cell donor, typically a human leukocyte antigen (HLA) matched sibling donor. Unfortunately, only an estimated 18% of patients with SCD have a suitable donor.[18] Also, there are significant risks associated with allo-HSCT,

including graft failure, graft-versus-host disease (GVHD), severe infection, hematologic malignancy, bleeding events, and death.[19, 20]

Patients who undergo allo-HSCT also have a risk of hematologic malignancy post-transplant, particularly with non-myeloablative conditioning regimens and/or in the setting of graft failure.[21] Allo-HSCT approaches using alternative donors, such as matched unrelated donors or haploidentical donors, remain investigational with these approaches having even higher risks, particularly those associated with GVHD, graft failure, and death.[20, 22] Thus, allo-HSCT, despite the potential to be curative for patients with severe SCD, is not widely used.

The development of exa-cel is grounded in human genetics showing that fetal hemoglobin (HbF) can substitute for sickle globin in erythrocytes and mitigate the clinical consequences of SCD. HbF is an endogenous globin normally expressed during fetal development and in the neonatal period. Neonates and infants with SCD are asymptomatic as long as their HbF levels remain high, with symptoms only developing when HbF is replaced by sickle globin in the first year after birth. Variants in multiple genes including BCL11A, a repressor of the HbF gene, have been found that increase HbF and reduce the severity of clinical consequences of SCD.[14, 23-26] Patients with SCD who coinherit hereditary persistence of fetal hemoglobin (HPFH), in which HbF expression remains high into adulthood (> 20% HbF) have little or no disease and are generally healthy including absence of VOCs.[27-29]

Exa-cel was developed as a one-time treatment that could provide a potential functional cure for patients with severe SCD. The mechanism of action of exa-cel is an *ex-vivo* CRISPR/Cas9-mediated gene edit of the intronic erythroid-specific enhancer of *BCL11A*. The genomic target was selected as optimal because (a) edits at this erythroid specific enhancer downregulate *BCL11A* expression only in the erythroid lineage, (b) this intronic location is > 25 kb from any protein coding region and (c) the specific target DNA sequence is unique in the genome, minimizing potential for off-target editing. Consistent with this mechanism and site of action, comprehensive non-clinical studies did not identify any off-target editing by exa-cel. Moreover, exa-cel's gene editing mechanism of action leads to persistent and irreversible reactivation of HbF expression in erythroid cells regardless of age, sex, race, or SCD disease genotype.

The exa-cel development program in SCD consists of Study 121, a pivotal Phase 1/2/3 study, and Study 131, a long-term safety and efficacy follow-up study. The pivotal study included pre-specified interim analyses (IA), and as described in this briefing document, the Sponsor proposes the data support either traditional or accelerated approval by the FDA.

The primary efficacy endpoint in Study 121 was absence of severe VOCs for at least 12 consecutive months (VF12) to support a traditional approval. The study also included evaluation of a surrogate efficacy biomarker, HbF (%) ≥ 20% at Month 6, and an interim clinical endpoint (ICE), absence of severe VOCs for at least 9 consecutive months (VF9), to support accelerated approval. These endpoints are described in greater detail in Section 1.3.1. For context, accelerated approval is a pathway allowing drugs for serious diseases that fulfill an unmet medical need to be approved faster than a traditional pathway. As described, severe SCD is a severe disease with high unmet need and thus meets these criteria.

The pivotal study, Study 121 met the primary efficacy endpoint of VF12: 29 of 30 (97%) patients in the primary efficacy set (PES) achieved VF12. Study 121 also met the key secondary

endpoint of free from inpatient hospitalization for severe VOCs for at least 12 consecutive months (HF12): 30 of 30 (100%) patients in the PES achieved HF12. These data are transformational given that 1) these patients had an average of 3.9 VOC per year over the previous 2 years, and 2) spontaneous remission of VOCs rarely occurs in patients with recurrent VOC per the 121 study eligibility criteria (2 or more VOC in the each of the prior 2 years).[30] In addition, transformational benefit is also demonstrated by 30 of 30 patients who were hospitalization free for 12 consecutive months, given that on average these patients had 2.7 hospitalizations per year and spent 17.1 days per year in the hospital over the previous 2 years. Data to support accelerated approval were similarly strong. Specifically, 40 of 40 (100%) patients achieved the surrogate efficacy biomarker of HbF ≥ 20% at Month 6, which was highly predictive of clinical benefit in eliminating VOC and achieving VF12. As mentioned above, natural history studies of SCD patients with HPFH demonstrate that patients with HbF levels over 20% are generally healthy and do not experience VOC. Finally, 31 of 32 (97%) patients achieved the intermediate clinical endpoint (ICE) of VF9, an endpoint that has been shown to predict longer term efficacy. Both surrogate endpoints are strongly supportive of accelerated approval.

Data included in the BLA consists of 44 patients dosed with exa-cel and followed for a median of 19.3 months and a mean of 20.1 months. The longest follow-up is 48.1 months with 30 patients having at least 18 months of follow-up post exa-cel treatment. The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk identified.

Taken together, the results from the exa-cel program in severe SCD are unprecedented. Exa-cel has demonstrated transformative efficacy, a strong safety profile, and a highly positive benefit-risk for treatment of severe SCD patients.

Post approval, to ensure safe use of exa-cel, the Sponsor considers product labeling (USPI and patient information) to communicate the relevant safety information for use of exa-cel and post-marketing pharmacovigilance (PV) surveillance to be sufficient and appropriate. In addition to standard post marketing PV surveillance, the Sponsor's PV program includes follow-up of patients enrolled and dosed in Study 121 for 15 years in the long term follow-up study (Study 131), as well as a proposed post-approval 15-year registry-based study to follow patients treated with commercial product.

This document is submitted in support of Sponsor's application for marketing approval of exa-cel to treat patients with SCD ages ≥ 12 years who have recurrent VOCs.

1.2 Product Development Rationale

1.2.1 Product Description

Exa-cel is a cellular product consisting of autologous $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) that are collected from the patient during apheresis and modified *ex-vivo* by highly specific CRISPR/Cas9-mediated gene editing of the intronic erythroid-specific enhancer region of the *BCL11A* gene. Specifically, the CRISPR-Cas9 components are introduced into the $CD34^+$ stem cells by electroporation and the resultant gene edited exa-cel drug product is cryopreserved and tested for release for patient dosing (Section 3.5).

Exa-cel is a single-dose intravenous treatment that is administered after fully myeloablative conditioning. The minimum recommended dose of exa-cel is 3×10^6 $CD34^+$ cells/kg. After successful engraftment of exa-cel, the precise, permanent, and irreversible *ex-vivo* edit results in increased production of HbF to levels that have been demonstrated to prevent VOCs and are protective against complications from SCD (Section 3.3). There is no known or hypothesized mechanism whereby a DNA edit would revert to reduce the reactivation of HbF after exa-cel treatment. The long-term engraftment of edited cells also demonstrates the successful editing of long-term HSCs that are known to persist for a person's lifetime.

The proposed indication is for the treatment of SCD in patients 12 years and older with recurrent VOCs. An indication for treatment of transfusion-dependent β-thalassemia (TDT) in patients of the same age is also being sought under a separate BLA application.

1.2.2 Rationale for Development of Exa-cel

The discovery and development of exa-cel is grounded in human genetics. Reactivation of HbF can result from inherited changes in multiple genes that lead to improvement in symptoms of SCD. Patients with SCD who co-inherit HPFH mutations, in whom HbF expression continues at a high level throughout adulthood, have little or no disease symptoms and are generally healthy. Patients with SCD-HPFH who have HbF levels above 20%, rarely, if ever, experience VOCs.[14, 27, 28] Specifically, when HbF accounts for ≥ 20% of total Hb, disease complications are reduced.[14, 27, 28, 31] Naturally occurring common genetic variants in the intronic erythroid specific enhancer of *BCL11A* were also found to increase HbF levels resulting in decreased severity of SCD in population-based human genetic studies.[9, 23, 26, 32]

Mechanistic studies[33, 34] identified that disruption of the intronic erythroid specific enhancer of the *BCL11A* gene results in reduction in BCL11A protein levels only in maturing RBCs. This reduction in BCL11A protein levels leads to increased HbF production. The specificity of the erythroid specific target is shown by studies examining genetic variability at the intronic region of the *BCL11A* erythroid specific enhancer showing the absence of any other phenotype.[35] The exa-cel program was designed to use CRISPR-Cas9 and a highly specific guide sequence that has no off-target effects, precisely editing the site of the naturally occurring genetic variant in the *BCL11A* enhancer that is associated in human populations with increased HbF and reduced SCD severity. The editing process is performed *ex-vivo* in only $CD34^+$ cells and is transient, so there is no residual gene editing activity in the cells delivered to the patient.

1.2.3 Regulatory Considerations

The clinical development program in SCD includes one pivotal Phase 1/2/3 study (Study 121) and one long-term follow-up study (Study 131). Both studies were designed in consultation with the Agency: Study 121 has a sample size of approximately 45 patients and is 2 years in duration. Study 131 is the long-term follow-up study designed to evaluate patients who roll over from Study 121 and provides a total of up to 15 years of follow-up after exa-cel infusion (Section 4.1 Table 5). Study 121 has completed enrollment and dosing of all planned patients (46 patients in total). Follow-up in both studies (Study 121 and Study 131) is ongoing.

The clinical data package submitted with the initial BLA included data from a prespecified interim analysis 2 (IA2; data cutoff date 10 February 2023), which included 20 patients with at

least 16 months of follow-up in the PES. Results at IA2 were alpha-protected from family-wise type-1 error and crossed statistical significance thresholds for the primary and both key secondary endpoints, establishing statistically significant efficacy when tested against a prespecified null hypothesis of 50%.

An updated data analysis, based on a 14 June 2023 data cutoff, was requested by FDA. In this updated data set, 30 patients with at least 18 months of follow-up were included in the PES and were available for evaluation of the primary efficacy endpoint. Data from the updated data cutoff was highly consistent with the initial BLA and are presented in this briefing document.

Exa-cel has received Fast Track, Orphan Drug Designation, Regenerative Medicine Advanced Therapy (RMAT) Designation, Rare Pediatric Disease Designation, and Priority Review for the treatment of SCD. Throughout the clinical program, the Sponsor has engaged with FDA for alignment on many key elements, including trial design, sample size, definitions of clinically meaningful endpoints, and statistical analysis plans (Section 4.2).

Prior to submission of the Biologics License Application (BLA), the FDA encouraged the Sponsor to submit all data and justification to support either traditional or accelerated approval. The data for traditional approval are based on 29 of 30 (97%) patients achieving the primary endpoint (VF12) with at least 18 months of follow-up and supported by the key secondary and additional endpoints. The data for accelerated approval are based on 40 of 40 (100%) patients achieving the surrogate efficacy biomarker of HbF ≥ 20% at Month 6, and 31 of 32 (97%) patients achieving the ICE, defined as proportion of patients who have not experienced any severe VOC for ≥ 9 consecutive months (VF9) (Sections 7.2.4 and 7.2.10). Per FDA guidance, if a drug is approved via an accelerated pathway, the Sponsor must complete a confirmatory trial to verify the clinical benefit. For exa-cel, the requirement for the completion of a confirmatory trial can be met by completion of Study 121, which is fully enrolled and has dosed all patients. Final data for Study 121, which follows patients for a two-year period, will be available the second half of 2025.

1.3 Clinical Development Program and Results

The exa-cel clinical development program was designed with the goal of eliminating VOCs and thereby offering a one-time, potential functional cure for severe SCD. The program consists of Study 121, a Phase 1/2/3 single arm study of ~45 patients with two years of follow-up and Study 131, a 15-year long-term follow-up study for patients who roll-over from Study 121. The clinical development program was initiated in 2018. Study 121 is a global study and includes 15 sites. The efficacy results included in the BLA consist of 30 patients treated with exa-cel in Study 121 and followed for a minimal duration of 18 months, a median duration of 26 months, and a maximum duration of 48.1 months, including follow-up in Study 131. Seventeen patients have rolled into Study 131 and have a median follow-up duration after exa-cel infusion of 28.3 months. The Sponsor proposes the efficacy, safety, and benefit-risk profile of exa-cel as demonstrated in Study 121 and Study 131 support either traditional or accelerated approval, and seeks an indication for exa-cel for the treatment of severe SCD in patients 12 years of age and older with recurrent VOCs.

1.3.1 Study 121/131 Design

Study 121 is a pivotal, single-arm, open-label, global Phase 1/2/3 study for patients ages ≥ 12 to ≤ 35 years who have SCD with recurrent VOCs (Section 7.1.1; Figure 7). The study follows patients for 2 years after exa-cel infusion. Evaluation of the primary and two key secondary endpoints starts 60 days after last RBC transfusion for post-transplant support or SCD management.

Study 121 is performed in four stages (Figure 7, See Section 7.1.1.1):

- **Stage 1**: screening and premobilization, including prophylactic RBC exchange or simple transfusions for ≥ 8 weeks before mobilization and conditioning to maintain HbS < 30% to minimize SCD-related complications or VOCs during mobilization/apheresis and peri-transplant, in accordance with recommended HSCT and gene therapy protocols.
- **Stage 2**: mobilization with plerixafor, autologous $CD34^+$ cell collection via apheresis, and exa-cel manufacture.
- **Stage 3**: myeloablative conditioning with pharmacokinetically adjusted busulfan for 4 consecutive days, followed by exa-cel infusion (Study Day 1).
- **Stage 4**: in-hospital follow-up until neutrophil engraftment, followed by outpatient follow-up for approximately 2 years after exa-cel infusion.

Patient selection for Study 121 included a requirement that participants had ≥ 2 severe VOC events per year during each of the 2 years immediately before study screening, while receiving appropriate supportive care. Severe VOCs were defined as any one of the following events:

- Acute pain that requires a visit to a medical facility and administration of pain medications (opioids or non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
- Acute chest syndrome (ACS), as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
- Priapism lasting > 2 hours and requiring a visit to a medical facility
- Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥ 2 g/dL.

In this document from here on the term “severe VOC” will be referred to as “VOC” for clarity. VOCs in the 2 years prior to screening and after exa-cel infusion were adjudicated by an independent adjudication committee.

Patients with β^S/β^S, β^S/β^0, or β^S/β^+ genotypes were eligible to enroll, and exa-cel’s mechanism of action was expected to provide clinical benefit irrespective of genotype.

Endpoints assessed in Study 121 were discussed and aligned with FDA and are presented in Table 1, as grouped according to their clinical manifestation in SCD (See Section 7.1.1.3).

Table 1: Efficacy Endpoints for Study 121

Endpoint Group:	Description
VOC-related endpoints	
Primary Endpoint (VF12)[a]	Proportion of patients who have not experienced any severe VOC for at least 12 consecutive months after exa-cel infusion, starting 60 days after the last RBC transfusion for post-transplant support or SCD management. Patients with ≥ 16 months of follow-up are evaluable for this endpoint.
Second Key Secondary Endpoint (VF9)	Proportion of patients who have not experienced any severe VOC for at least 9 consecutive months at any time after exa-cel infusion, starting 60 days after last RBC transfusion for post-transplant support or SCD management. Patients with ≥ 12 months of follow-up are evaluable for this endpoint. VF9 was assessed as an intermediate clinical endpoint (ICE)
Secondary Endpoint	Duration of VOC-free in patients who achieve the primary endpoint of VF12
Hospitalization-Related Endpoints	
First Key Secondary Endpoint (HF12)	Proportion of patients free from inpatient hospitalization for severe VOCs sustained for at least 12 months after exa-cel infusion, starting 60 days after the last RBC transfusion for post-transplant support or SCD management. Patients with ≥ 16 months of follow-up are evaluable for this endpoint.
Hematologic Parameters	
Secondary Endpoints	• HbF as percentage of total Hb (HbF [%]) over time, including HbF (%) ≥ 20% at Month 6 (surrogate efficacy biomarker) • Levels of total Hb and HbF over time • Reductions from baseline in the number of annualized RBC transfusions • Measures of hemolysis
Exploratory Endpoint	Changes in the proportions of F-cells over time
Allelic Editing	
Secondary Endpoint	Proportion of alleles with intended genetic modification in peripheral blood leukocytes and $CD34^+$ cells of the bone marrow over time
Patient-Reported Outcomes (All Secondary Endpoints)	
Adults (ages ≥ 18 years)	• Pain-scale: 11-point Numeric Rating Scale (NRS) • Functional Assessment of Cancer Therapy — Bone Marrow Transplant (FACT-BMT) • Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) • EuroQol Questionnaire-5 dimensions-5 levels of severity (EQ-5D-5L)
Adolescents (ages 12 to <18 years)	• Pain-scale: 11-point Numeric Rating Scale (NRS) • Pediatric Quality of Life Inventory (PedsQL) — teen self-report and parent proxy versions • PedsQL Sickle Cell Disease Module — teen self-report and parent proxy versions • EuroQol Questionnaire-5 dimensions-5 levels of severity youth version (EQ-5D-Y) — self-report and parent proxy versions

Hb=hemoglobin; HbF=fetal hemoglobin; RBC=red blood cell; SCD=sickle cell disease; VOC=vaso-occlusive crisis.
a. VF12 estimate was compared against a null response rate of 50%, selected based on the 3-year event free survival in patients without a matched related donor and only could receive haplo- or matched unrelated donor transplant, a proportion that is approximately 50%. Thus, this response rate was utilized for the null comparison on all primary and key secondary efficacy analyses.
Efficacy endpoints include endpoints discussed in this document.

Primary and key secondary efficacy endpoints were assessed in Study 121 in a hierarchical manner: VF12 (primary), followed by HF12 (first key secondary), then VF9 (second key secondary). The overall type I error rate was controlled accounting for interim and final analyses and multiple tests of primary and key secondary endpoints (See Section 7.1.1.4.3).

Study 121 included three analysis sets:

- **Full Analysis Set** (FAS) included all patients who received exa-cel infusion.
- **Primary Efficacy Set** (PES) is subset of the FAS defined as patients who are evaluable for the primary endpoint (VF12; 12 consecutive months without a VOC) who have been followed for at least 16 months after exa-cel infusion. The 16-month follow-up was included because the evaluation of VF12 starts 60 days after the last RBC transfusion for post-transplant support or SCD management which allows for the expected post-transplant transfusions. Patients who had less than 16 months follow-up due to death or discontinuation due to adverse events (AEs) related to exa-cel were also included in this set. Importantly, at the request of the Agency the primary endpoint was also evaluated when patients reached at least 18 months of follow-up after exa-cel infusion.
- **Early Efficacy Set** (EES) was defined as a subset of the FAS that includes patients who are evaluable for VF9 (9 consecutive months without a VOC) who have been followed for at least 12 months after exa-cel infusion. The evaluation of VF9 started 60 days after the last RBC transfusion for post-transplant support or SCD management. Patients who had less than 12 months of follow-up due to death or discontinuation due to AEs related to exa-cel were also included in this set. This set was used for the evaluation of VF9 as an intermediate clinical endpoint (Section 7.1.1.3 and Section 7.1.1.4.2 for a complete listing of analysis sets and endpoints assessed).

Study 131 is an ongoing long-term follow-up study for patients who received exa-cel infusion in Study 121 and will provide up to a total of 15 years of follow-up after exa-cel infusion. The primary endpoints of Study 131 are safety related (new malignancies, new or worsening hematologic disorders, mortality, and adverse events). Secondary endpoints of Study 131 include efficacy measures that provide longer follow-up of endpoints assessed in Study 121 described above (See Section 7.1.2 for additional details). Analysis that includes data from both Study 121 and Study 131 is referred to as the SCD[PES] for patients who were evaluable for the primary endpoint and SCD[FAS] for all patients who received exa-cel.

1.3.2 Study 121/131 Efficacy Results

Results from Studies 121 and 131 demonstrated transformational, consistent, and durable clinical benefit. In Study 121, all primary and key secondary endpoints showed overwhelming clinical benefit, as measured by both elimination of VOC events and freedom from VOC-related hospitalizations among patients with severe SCD. Findings were statistically significant at the prespecified IA2 (data cutoff date of 10 February 2023; all p-values < 0.0001) and are wholly supported by results from the 14 June 2023 additional data cutoff requested by the FDA. Durability of the efficacy response was confirmed in Study 131 with additional follow-up informing the duration VOC-free and duration of freedom from VOC-related hospitalizations.

Primary Endpoint

Study 121 met its primary endpoint of VF12: 29 of 30 (96.7%) patients in the PES achieved VF12 (95% CI: 82.8%, 99.9%; 1-sided p < 0.0001 [against a 50% response rate]) (Table 2; Section 7.2.3). The magnitude of this treatment effect is transformational. Patients with severe SCD who have recurrent VOCs over a multiple year period are highly unlikely to spontaneously remit. Given that the patients in the PES had a mean of 3.9 VOCs per year in the previous 2 years prior to screening, achieving VF12 in 96.7% of patients is highly clinically meaningful. The mean (SD) follow-up duration of patients in the PES was 25.6 (7.29) months after exa-cel infusion, including follow-up in Study 131.

Table 2: Primary Endpoint Results: Proportion of Patients Who Achieved VF12 (Study 121, PES)

Primary Endpoint, n (%)	PES N=30
Proportion of Patients who achieved VF12	29 (96.7)
2-sided 95% CI	(82.8, 99.9)
1-sided p-value[a]	< 0.0001[a]

EAC=endpoint adjudication committee; exa-cel=exagamglogene autotemcel; IA=interim analysis; N=total sample size; n=size of subsample; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VF12=absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion; VOC=vaso-occlusive crisis.
Notes: The evaluation of VF12 started 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The prohibited medication treatment period was excluded from the VOC-free duration. The percentage of patients who achieved VF12 was calculated relative to the number of patients in the PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.
a. Statistical significance was established at IA2; this was against a 50% response rate.

Key Secondary Endpoint: HF12

Study 121 also met the first key secondary endpoint (HF12) which measures VOCs that lead to in-patient hospitalization. Specifically, 30 of 30 (100%) patients in the PES achieved HF12 (95% CI: 88.4%, 100%; 1-sided p < 0.0001 [against a 50% response rate]) (Table 3; Section 7.2.4.1).

Patients in the PES had a mean (range) of 2.7 (0.5 to 8.5) inpatient hospitalizations for severe VOCs per year with a mean (range) duration of 17.1 (2.0 to 64.6) days of inpatient hospitalizations per year in the 2 years prior to screening (Table 10; Section 7.2.2); therefore, all patients being free from inpatient hospitalization for at least 12 months is highly clinically meaningful.

Table 3: First Key Secondary Endpoint Results: Proportion of Patients Who Achieved HF12 (Study 121, PES)

Patients Achieving HF12, n (%)	PES N=30
Proportion of Patients who achieved HF12	30 (100)
2-sided 95% CI	(88.4, 100)
1-sided p-value[a]	< 0.0001[a]

Exa-cel=exagamglogene autotemcel; HF12=free from inpatient hospitalization for severe VOCs for at least 12 months after exa-cel infusion; IA=interim analysis; N=total sample size; n=size of subsample; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VOC=vaso-occlusive crisis.
Notes: The evaluation of HF12 started 60 days after last RBC transfusion for post-transplant support or SCD gate management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The prohibited medication treatment period was excluded from the HF duration. The percentage of patients who achieved HF12 was calculated relative to the number of patients in the PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.
a. Statistical significance was established at IA2; this was against a 50% response rate.

Hematologic Parameters and Allelic Editing

The primary and key secondary endpoints are supported by hematologic parameters and evidence of allelic editing in the bone marrow and peripheral blood. After exa-cel infusion, HbF (%) increased rapidly. The mean HbF (%) reached >40% by Month 6. Individual patient HbF (%) levels were stable through the duration of follow-up (Section 7.2.6; Figure 11; Section 7.2.6.2; Figure 13). These levels are well above 20% HbF that has been shown to be protective and prevent VOCs.[14, 27, 28, 36] After exa-cel, HbF was pancellular, being present in ≥90% of circulating RBCs, as measured by F-cells, which are circulating RBCs expressing detectable levels of HbF, demonstrating broad protection of RBCs by exa-cel.

High and stable allelic editing was also observed through the duration of follow-up (Section 7.2.7; Figure 14; Figure 15). Overall, allelic editing data in the bone marrow and peripheral blood indicate durable engraftment of edited long-term hematopoietic stem cells (LT-HSCs) and reflect the permanent nature of the edit at the intronic erythroid-specific enhancer of the *BCL11A* gene.

Hemolysis Measures

Reduction in hemolysis is an additional measure of benefit following exa-cel treatment. In SCD, RBCs are prone to hemolysis which is associated with significant morbidity and mortality.[13, 37] The dominant mechanism of hemolysis in SCD, intravascular hemolysis, is measured by lactate dehydrogenase (LDH) and haptoglobin. Decreased LDH and increase to detectable levels of haptoglobin indicate improvements in hemolysis.[38, 39] Mean LDH levels normalized by Month 9 and all patients with follow-up data generally had detectable and durable haptoglobin levels after Month 6 (Sections 7.2.8.1 and 7.2.8.2). Taken together, these results indicate that exa-cel confers broad protection of RBCs and the resolution of hemolysis.

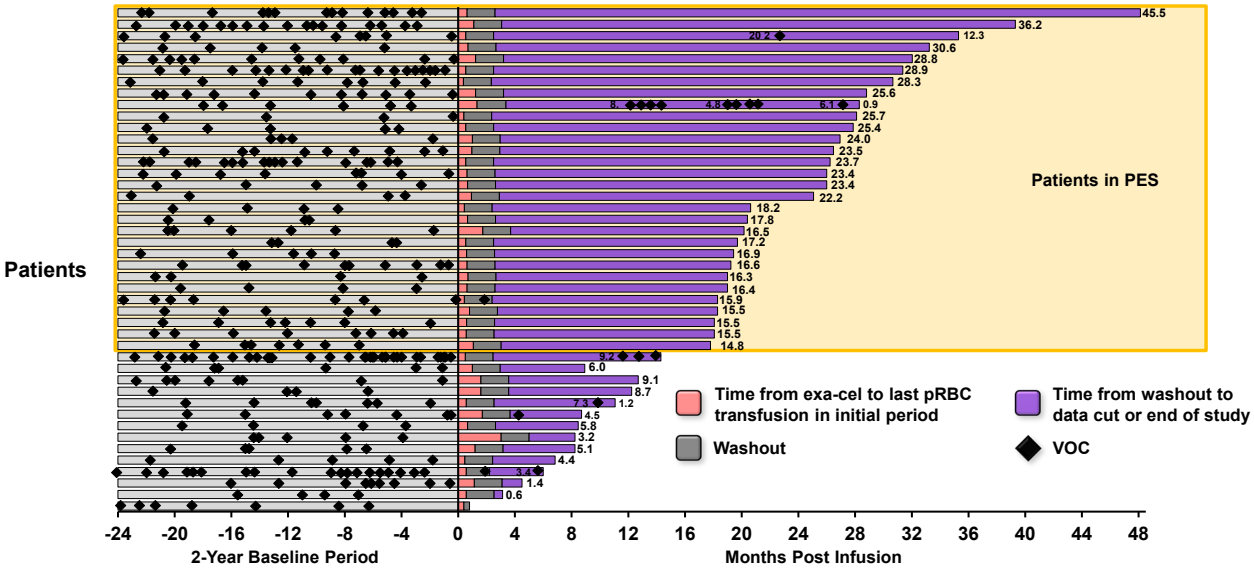
Patient-Reported Outcomes

Additionally, results from multiple patient-reported outcomes (PROs) indicated substantial and clinically meaningful improvement across all instruments and domains. PROs demonstrated clinically meaningful and substantial improvement across all instruments including those specific to general well-being, HSCT, and SCD. Assessments of PRO domains related to general health, physical, emotional, social, and functional well-being all demonstrated improvement. In addition, all pain-related PRO scores improved, including clinically meaningful improvement in pain numeric rating scale (NRS) and in the Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) pain subscales (Section 7.2.9).

Long-Term Response

Long term response following exa-cel treatment was also assessed in the clinical development program and the data demonstrate long term durability (See Section 7.2.5). As described above, exa-cel led to the engraftment of LT-HSCs edited at the BCL11A intronic erythroid specific enhancer, resulting in durable expression of HbF. This is expected, given that genome editing of DNA is permanent and that stable engraftment has occurred, with LT-HSCs known to persist for the lifetime of an individual. Clinical efficacy was consistent with this and was durable: for the 29 of 30 patients who achieved VF12, the mean (SD) VOC-free duration was 22.4 (7.2) months, with total VOC free duration of up to 45.5 months (Figure 1 and Section 7.2.5.1). All patients in the PES remained free from inpatient hospitalization for VOCs for up to 45.5 months, starting 60 days after the last RBC transfusion, except for one patient. This patient was hospitalized nearly 23 months after exa-cel infusion in the context of acute parvovirus B19 infection after achieving VF12 and HF12. Parvovirus B19 is known to cause severe, life-threatening infections in SCD patients often resulting in profound anemia due to parvovirus associated RBC aplasia typically requiring prolonged RBC transfusion support, prolonged hospitalization often in an intensive care unit, and increased risk of ACS and life-threatening complications.[40] In contrast, this exa-cel treated patient recovered uneventfully from the documented Parvovirus B19 infection within a few days without any complications and without the need for RBC transfusion indicating the protection from severe complications provided by exa-cel. Following recovery from the parvovirus infection, the patient has remained VOC-free and hospitalization free through 12.3 months of follow-up after the event through the data cutoff for analysis (Section 7.2.5.3.1).

Figure 1: Duration of Severe VOC-Free Period for Individual Patients (Studies121 and 131, [SCD]FAS)

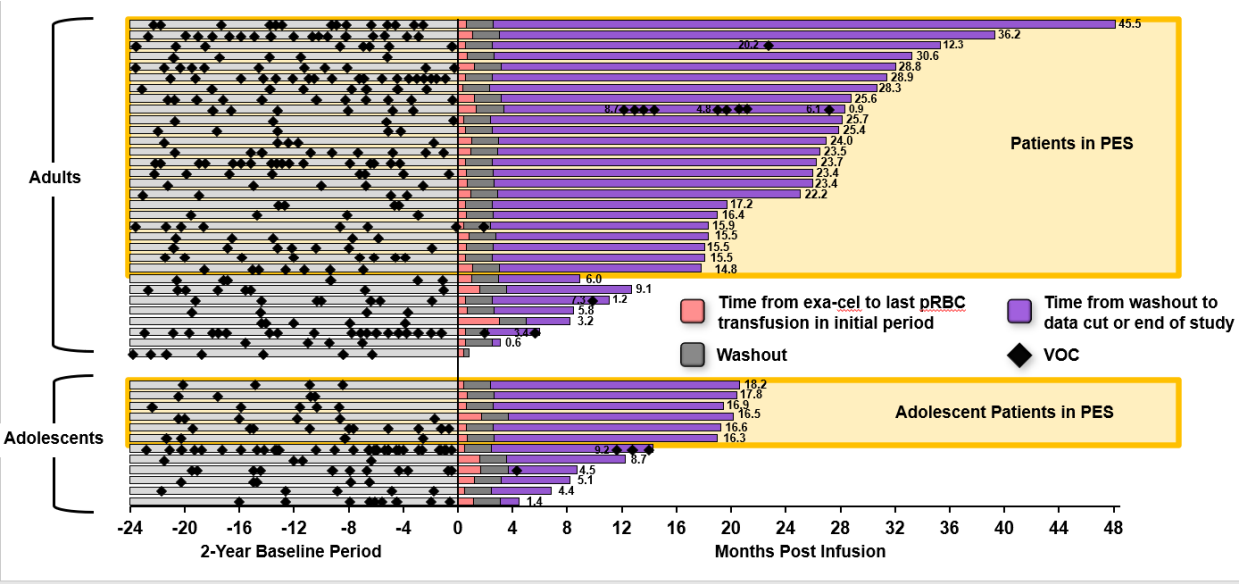


EAC=adjudication endpoint committee; exa-cel=exagamglogene autotemcel; [SCD]FAS=Full Analysis Set including data from Study 121 and Study 131; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VOC=vaso-occlusive crisis.
Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria were included. Severe VOC free duration starts 60 days after the last RBC transfusion for post-transplant support or SCD management. The numbers to the right of the purple bars indicate the duration of VOC free starting 60-day after last RBC transfusion or from the last VOC. and this duration is indicated by the numbers to the right of the purple bars. The RBC washout period refers to the duration of 60 days after the last RBC transfusion for post-transplant support or SCD management.

Efficacy in Subgroups

The efficacy results were consistent across age groups, including adolescents (ages 12 to <18 years), sex, race, and disease genotype (Section 7.2.11). Key secondary and secondary endpoints also showed clinically meaningful improvements and demonstrated overall benefit of exa-cel treatment, including elimination of transfusions and improvement in hemolysis assessments. In adolescents, exa-cel demonstrated consistent clinical benefit similar to adults, as expected based on the similar disease pathophysiology and exa-cel mechanism of action in reactivating HbF. Adolescents represented a significant percentage of the patient population for evaluation of treatment effect (Figure 2): 12 adolescent patients received exa-cel, representing ~30% of all patients who have received exa-cel, with 6 adolescents being evaluable for the primary efficacy endpoint, representing 20% of evaluable patients. All adolescent patients evaluable for the primary endpoint (6 of 6 [100%]) achieved VF12 and HF12.

Figure 2: Duration of Severe VOC-Free Period for Individual Adolescent and Adult Patients (Studies 121 and 131, [SCD]FAS)



EAC=Endpoint Adjudication Committee; exa-cel=exagamglogene autotemcel; [SCD]FAS=Full Analysis Set including data from Study 121 and Study 131; SCD=sickle cell disease; PES=Primary Efficacy Set; RBC=red blood cell; VOC=vaso-occlusive crisis.
Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria were included. Severe VOC-free duration starts 60 days after the last RBC transfusion for post-transplant support or SCD management. The numbers to the right of the purple bars indicate the duration of VOC free starting 60-day after last RBC transfusion or from the last VOC. The RBC washout period refers to the duration of 60 days after the last RBC transfusion for post-transplant support or SCD management.

Surrogate Efficacy Biomarker and Intermediate Clinical Endpoint in Support of Accelerated Approval

HbF (%) ≥ 20% at 6 months and VF9 were assessed as a surrogate efficacy biomarker and an ICE reasonably likely to predict clinical benefit of VF12. Epidemiology and real-world evidence data support that elevated HbF ≥ 20% is predictive of clinical benefit, specifically in avoiding VOC.[7, 14, 28, 36] Real-world evidence studies (using Medicaid data and Center for International Blood and Marrow Transplant Research [CIBMTR] data[41]) from patients with SCD after allo-HSCT support that VF9 is predictive of VF12. In Study 121, 40 of 40 (100%) patients met the surrogate biomarker endpoint of HbF (%) ≥ 20% at 6 months including 11 of 11 (100%) adolescents and 31 of 32 (97%) patients met the endpoint of VF9, including 7 of 7 (100%) adolescents. Results from the surrogate biomarker and ICE endpoints are robust and can strongly support accelerated approval.

Efficacy Conclusions

Overall, the totality of exa-cel efficacy data across the primary, key secondary, and secondary endpoints show transformational and durable clinical benefit, regardless of age, sex, race, or disease genotype. Adolescent patients (ages 12 to <18 years) demonstrated similar responses to adult patients (ages 18 to 35 years). Clinical findings are supported by increases in HbF (%), F-cells (%), and evidence of stable allelic editing, which were also consistent across age

groups. Further support for overall clinical efficacy was shown by consistent improvement in patient reported outcomes, which demonstrated substantial clinically meaningful and sustained improvements.

Additionally, analyses comparing results in the PES show that early response predicts long-term efficacy: hematologic response (HbF [%] ≥ 20% at 6 months) and clinical response (VF9) can serve as surrogate and intermediate clinical endpoints that predict for efficacy at 12 months and beyond.

In conclusion, the totality of efficacy data demonstrates transformational and consistent benefit for both adolescents and adults and supports either traditional or accelerated approval in both age groups.

1.3.3 Safety Results

The safety of exa-cel has been comprehensively evaluated in non-clinical and clinical studies, both of which demonstrated a favorable safety profile.

Extensive off-target assessment in $CD34^+$ samples from both healthy donors and SCD patients revealed no detectable off-target edits or evidence of chromosomal abnormalities following treatment with exa-cel. Clinically, exa-cel was generally safe and well tolerated among the 44 patients with SCD who received treatment with exa-cel infusion. The safety profile of exa-cel treatment was consistent with the use of busulfan for myeloablative conditioning and autologous HSCT, with delayed platelet engraftment the only exa-cel specific risk (Section 8). The safety of exa-cel was also consistent across adult and adolescent sub-groups.

1.3.3.1 Summary of Nonclinical Findings

Results from the nonclinical pharmacology, pharmacokinetics (PK), and toxicology studies demonstrate a favorable benefit-risk profile, and demonstrated (Section 5):

- No evidence of chromosomal abnormalities or translocations.
- No evidence for off-target editing in healthy volunteer or SCD patient $CD34^+$ samples
- No evidence for induction of the innate immune response was seen when $CD34^+$ cells were genetically modified with CRISPR/Cas9
- No adverse findings, tumorigenicity, or unwanted biodistribution to non-target tissues in NSG mice at a higher dose than was assessed in human clinical trials.

1.3.3.2 Summary of Clinical Findings

Adverse Events

In total, all 46 severe SCD patients in Study 121 have been dosed. As of the 14 June 2023 data cutoff date, 44 patients have received exa-cel, who provide 73.5 patient-years of exposure after exa-cel infusion (Section 8.1; Table 22). The most common AEs reported are identified in the busulfan prescribing information by Preferred Term (PT) or related medical concept (Table 24). The most common AEs (occurring in ≥ 40% of patients) after myeloablative busulfan conditioning and exa-cel infusion were nausea, stomatitis, vomiting, febrile neutropenia,

abdominal pain, headache, pruritus, decreased appetite, platelet count decreased, constipation, pain in extremity, arthralgia, and pyrexia.

The incidence of AEs was comparable between adolescent patients (ages 12 to <18 years) and adults (ages 18 to 35 years) (Section 8.5.1; Table 4).

No serious adverse events (SAEs) were considered as related or possibly related to exa-cel (Section 8.2.5; Table 28).

Table 4: Summary of Adverse Events From Exa-cel Infusion through 2 Years of Follow-up, Including by Age Group at Screening (Study 121, FAS)

	Age at Screening		
Adverse Events, n (%)	**12–<18 Years N=12**	**18-35 Years N=32**	**Total N=44**
Patients with any AE	12 (100)	32 (100)	44 (100)
AE related or possibly related to exa-cel	2 (16.7)	11 (34.4)	13 (29.5)
AE related or possibly related to busulfan	12 (100)	32 (100)	44 (100)
Grade 3/4 AE	10 (83.3)	32 (100)	42 (95.5)
SAE	5 (41.7)	15 (46.9)	20 (45.5)
SAE related or possibly related to exa-cel	0	0	0
SAE related or possibly related to busulfan	0	4 (12.5)	4 (9.1)
AE leading to study discontinuation	0	0	0
AE leading to death	0	1[a] (3.1)	1[a] (2.3)

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; n=size of subsample; SAE=serious adverse event;.
Notes: An AE missing relationship to busulfan/exa-cel is counted as related to busulfan/exa-cel.
a. Patient died of respiratory failure due to complications from COVID-19 that was considered unrelated to exa-cel.

There was 1 death (reported as not related to exa-cel and possibly related to busulfan), which was due to respiratory failure from COVID-19. Otherwise, no patient had an AE resulting in discontinuation after exa-cel infusion. There were no malignancies.

The safety profile was also generally consistent across subgroups, including age, race, region, sex, and disease genotype (Section 8.5).

Engraftment

All 44 (100%) of patients who have received exa-cel as of the 14 June 2023 data cutoff date achieved neutrophil engraftment by Study Day 43, the protocol-defined cut-off for successful engraftment. No patients had neutrophil engraftment failure, and none received backup $CD34^+$ cells (Section 8.4). All patients also achieved platelet engraftment, with 43 of 44 achieving platelet engraftment by the time of data cutoff for analysis and the remaining patient achieving platelet engraftment (subsequent to data cutoff) on Study Day 26.

The median (range) time to neutrophil engraftment was 27.0 (15, 40) days (Section 8.4.1; Table 29; Figure 18), which is consistent with the times to neutrophil engraftment observed in

the allo-HSCT literature as well as other genetic therapies. The median (range) time to platelet engraftment was 35.0 (23, 126) days (Section 8.4.2; Table 30; Figure 21), which is consistent with median times reported with other genetic therapies for SCD, however the median time to platelet engraftment is longer than those reported in allo-HSCT literature.[56, 113-116] As such, the Sponsor considers potential for longer time to platelet engraftment as a risk included as part of the Pharmacovigilance Plan (Section 8.11). There were no AEs of graft failure or graft rejection (Section 8.2).

Pharmacovigilance Plans

The sponsor proposes the following PV plans:

1. Product labeling describing exa-cel must be used in conjunction with busulfan myeloablative conditioning and HSCT and the attendant risks associated with this regimen as well as the exa-cel specific risk of delayed platelet engraftment.
2. Continuation of the long-term extension Study 131.
3. Establishment of a long-term registry-based study to follow patients treated with commercial exa-cel product post approval.

The totality of safety data demonstrates that exa-cel is safe and well tolerated in both adolescents and adults and supports a favorable benefit-risk in both populations. The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk. Otherwise, there were no additional exa-cel specific findings identified. Safety manifestations of myeloablation followed by exa-cel infusion are both monitorable and manageable by physicians and treatment centers with experience in HSCT. The proposed product information includes guidance and relevant information from the clinical trial experience, including AEs, SAEs, and engraftment.

The long-term safety of exa-cel will be further characterized in the ongoing Study 131, where patients who received exa-cel will be followed for a total follow-up of 15 years after treatment. Additionally, the Sponsor proposes patients treated with commercial exa-cel drug product post-approval will be followed for 15 years through a post-approval, registry-based, prospective study.

Post-marketing surveillance will be performed with the use of standard pharmacovigilance activities, including active follow-up of relevant clinical events (e.g., delayed neutrophil or platelet engraftment, and any hematologic malignancy).

In conclusion, the safety profile of exa-cel is generally consistent with that of myeloablative busulfan conditioning and HSCT. In combination with robust post-approval pharmacovigilance surveillance, including the ongoing long-term Study 131 and the proposed 15-year post-approval registry-based study to follow patients treated with commercial product, the product labeling (USPI and patient information) is considered appropriate to communicate the relevant safety information for use of exa-cel.

1.4 Summary

Exa-cel has been developed to treat SCD patients 12 years and older with recurrent VOCs. SCD is a rare disease affecting approximately 100,000 patients in the US. Severe SCD is even more rare affecting approximately 20,000 patients in the US. Severe SCD is a debilitating and life-shortening disease with a high unmet need, for which there are no broadly available, potentially curative options.

The efficacy of exa-cel is transformational and consistent across subgroups including age, sex, and disease genotype. Overall:

- 29 of 30 (96.7%) patients in the PES achieved VF12, including 6 adolescent patients
- 30 of 30 (100%) patients in the PES achieved HF12, including 6 adolescent patients

Results for the surrogate efficacy biomarker, HbF (%) ≥ 20% at 6 months and the ICE, VF9, are equally robust:

- 40 of 40 (100%) patients achieved the surrogate efficacy biomarker of HbF ≥ 20% at Month 6, including 11 adolescent patients
- 31 of 32 (97%) patients in the EES achieved the ICE, VF9, including 7 adolescent patients

The permanent, highly specific edit in exa-cel resulted in rapid, robust, and durable increase in HbF levels and F-cells. Mean HbF (%) production of approximately ≥40% from Month 6 was observed. As would be expected with the permanent nature of the highly specific edit, the increases in HbF were sustained throughout the duration of follow-up for all patients, demonstrating the durability of the treatment effect out to Month 48.

Allelic editing data in the bone marrow and peripheral blood indicate durable engraftment of edited LT-HSCs and reflect the permanent nature of the intended edit.

The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk. There were no clinically significant differences in observed AE profile between adult and adolescent patients (the same was observed for sex, race, and genotype).

Exa-cel has demonstrated transformative efficacy, a strong safety profile, and highly favorable benefit-risk for treatment of severe SCD patients ages 12 years and older. Based on these results, the Sponsor considers exa-cel appropriate for either traditional or accelerated approval.

2 BACKGROUND ON SICKLE CELL DISEASE

Summary

- SCD is an inherited hemoglobinopathy with high morbidity and mortality
  - The estimated lifespan for a person with SCD is 45 years of age, with higher risk of earlier mortality in severe SCD
  - In the US, over 90% of people with SCD are of African descent; people of Middle Eastern, Mediterranean, Indian, and Asian descent are also affected by SCD
  - Approximately 100,000 people in the US have SCD, of whom about 20,000 have severe disease
- Severe SCD is characterized by recurrent vaso-occlusive crises (VOCs), painful events driven by abnormal sickle Hb (HbS) resulting in obstruction of blood vessels
  - Recurrent VOCs culminate in progressive tissue damage in multiple end organs leading to progressive multi-organ damage and failure
- There are no approved therapies developed specifically to prevent VOCs for patients with severe SCD
  - Allo-HSCT can be curative, but only about 18% of patients have an HLA-matched sibling donor, and the procedure is associated with substantial risks, including chronic GVHD, primary/secondary graft failure, infections, and death

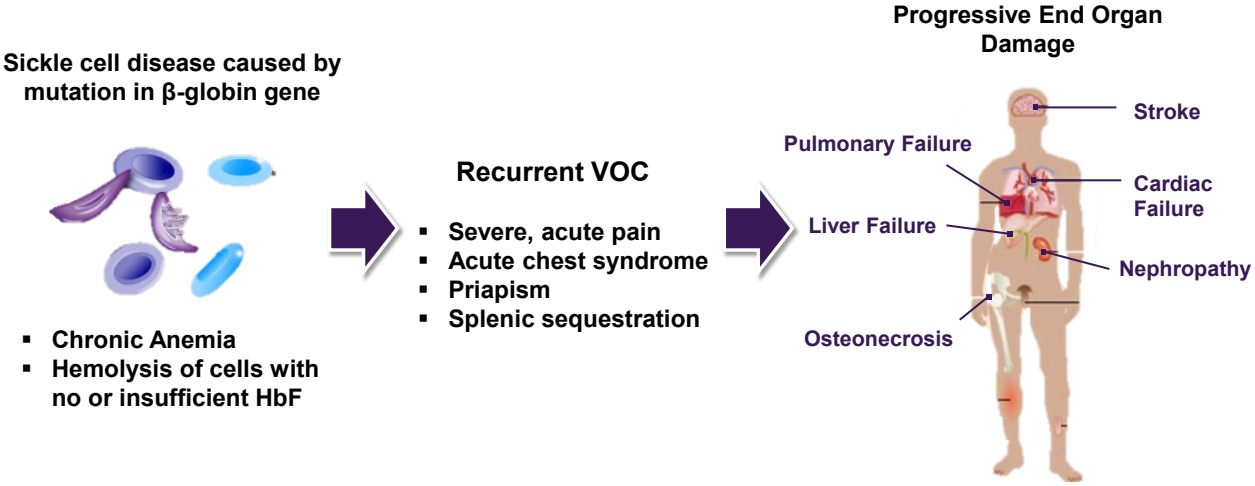
2.1 Sickle Cell Disease Background

Sickle cell disease (SCD) is an inherited genetic disorder whose clinical hallmark is recurrent painful vaso-occlusive crises (VOCs) which result in the high morbidity and mortality of the disease (Figure 3). SCD occurs at disproportionately high rates among individuals of African descent and, to a lesser extent, among individuals of Middle Eastern, Mediterranean, Indian, and Asian descent.[42, 43] In the US, over 90% of SCD patients are of African descent.[42, 43] The prevalence of SCD in the US has been reported as approximately 100,000 cases[5] and among these, approximately 20,000 have severe disease defined by recurrent VOC who would be considered for curative therapy.[30, 44-47]

SCD is caused by a single-nucleotide substitution in which the amino acid valine replaces glutamic acid at position 6 of the β-globin chain leading to abnormal sickle hemoglobin (HbS). The most prevalent form of SCD occurs due to the presence of homozygous HbS mutation (β^S/β^S genotype). However, SCD can also result from compound heterozygosity of one HbS mutation and one β-thalassemia mutation (i.e., β^S/β^0 or β^S/β^+ genotypes), or with another hemoglobin (Hb) variant (e.g., β^S/β^C). Importantly, individuals with all SCD genotypes can have severe disease as defined by recurrent VOC events because they share a common pathophysiology driven by HbS. In the deoxygenated state, HbS polymerizes producing abnormal, sickle-shaped red blood cells (RBCs) with limited flexibility, increased adhesive and inflammatory properties, and a predisposition to hemolysis. Sickle RBCs trigger painful VOCs and chronic hemolytic anemia. Chronic hemolytic anemia contributes to SCD morbidity, including increased hospitalizations, need for RBC transfusions, poor quality of life, as well as contributing to mortality.[39] VOCs result from blockages in small- to medium-sized blood vessels that deprive downstream tissues of nutrients and oxygen resulting in tissue infarction and

ischemia/reperfusion injury. VOC events culminate in progressive tissue damage in multiple end organs leading to their dysfunction, and ultimately failure.[10-12]

Figure 3: Overview of Sickle Cell Disease Pathology and Symptoms



HbF=fetal hemoglobin; VOC=vaso-occlusive crisis.

VOCs require care at a health care facility, with a subset requiring inpatient hospitalization. Painful VOC events are the most common cause of hospitalizations for individuals with SCD.[8, 46, 48, 49] VOCs result in approximately 100,000 hospitalizations per year in the US with an average length of hospital stay of 5.0 days.[50] Patients who have severe disease are at even greater risk of these disease complications and have worse outcomes, including increased mortality.[2-4, 7, 9, 51, 52]

Overall, SCD patient lifespan is shortened by 2 to 3 decades compared to the general population; the median age at death is 45 years, with some patients only surviving to 20 years.[2-4, 6, 9] Patients with severe disease have even greater morbidity and mortality, including increased mortality in adults and adolescents. [2-4, 7, 9, 52]

2.2 Unmet Medical Need

No currently approved product offers the potential for a cure for SCD, and there are no approved therapies that have been demonstrated to ameliorate disease complications in SCD patients with recurrent VOC who are at the highest risk for morbidity and mortality. The current approved treatments for SCD require chronic administration, are only partially effective and do not eliminate VOCs. HU provides modest efficacy and may reduce some complications of SCD; however, many patients have an insufficient response or are intolerant to HU treatment. HU has not been shown to eliminate VOCs.[15] Although two additional chronic therapies, voxelotor (Oxbryta®) and crizanlizumab (Adakveo®), were approved in 2019 for SCD; neither have efficacy in reducing or eliminating VOCs.[16, 17]

Allogenic hematopoietic stem cell transplantation (allo-HSCT) is a potential curative option for SCD, with the best outcomes being when allo-HSCT is performed with human leukocyte antigen (HLA)-matched sibling donors and when transplant is done at younger ages before accumulating SCD-related end-organ damage. However, only 18% of patients with SCD have

HLA-matched sibling donors, thus highlighting the unmet need for effective potentially curative therapies.[53] Also, there are significant risks associated with allo-HSCT, including graft failure, acute and chronic graft-versus-host disease (GVHD), severe infection, hematologic malignancy, bleeding events, and death. Chronic GVHD occurs at a frequency of up to 14% to 18% after allo-HSCT[19, 20, 54-56], with primary and secondary graft failure occurring at a frequency of up to 7% to 9%.[19, 20, 54] Allo-HSCT approaches using alternative donors, such as matched unrelated donors or haploidentical donors, remain investigational with these approaches associated with higher risks than matched sibling donor allo-HSCT, particularly for complications of GVHD, primary/secondary graft failure, and transplant-related mortality.[57]

In contrast, exagamglogene autotemcel (exa-cel) is a one-time potentially functional curative therapy with an autologous product that does not require an allogeneic donor. Exa-cel uses fully myeloablative conditioning and has shown high rates of engraftment. Because it is an autologous therapy, there is no acute and chronic GVHD or immunologic risks of secondary graft failure/rejection associated with allogeneic transplant. Finally, post-transplant immunosuppressive therapies are not needed.

3 PRODUCT DESCRIPTION

Summary

- The proposed indication for exa-cel is for the treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso-occlusive crises (VOCs)
- Exa-cel consists of autologous CD34$^+$ HSPCs, which are modified *ex-vivo* by CRISPR/Cas9
  - The recommended minimum dose is 3 × 10^6 CD34+ cells/kg
- Development of exa-cel is grounded in human genetics showing that elevated levels of HbF ≥ 20% are known to be protective against disease complications, including preventing VOCs
- The mechanism of action of exa-cel is to reactivate high levels of HbF via CRISPR/Cas9 gene editing targeting an intronic erythroid specific enhancer of the BCL11A gene
- The specific and irreversible edit reduces expression of BCL11A only in erythroid cells
  - BCL11A regulation and function in other cell types is unchanged
- CD34+ cells are edited using electroporation of a ribonucleoprotein (RNP) complex composed of the Cas9 nuclease and a highly specific guide RNA; a non-viral system
- Exa-cel has been extensively characterized for off-target editing, and no evidence of off-target editing has been observed

3.1 Proposed Indication

The proposed indication for exa-cel is for the treatment of SCD in patients 12 years and older with recurrent VOCs.

3.2 Drug Product

Exa-cel is a cellular product consisting of autologous CD34$^+$ HSPCs that are collected from the patient during apheresis and modified *ex-vivo* by highly specific CRISPR/Cas9-mediated gene editing of the intronic erythroid-specific enhancer region of the *BCL11A* gene.

Exa-cel is a single-dose intravenous (IV) treatment that is administered after fully myeloablative conditioning. The minimum recommended dose of exa-cel is 3 × 10^6 CD34$^+$ cells/kg. Because exa-cel is an autologous therapy, there is no identified maximum dose. The drug product is composed of 1 or more vials of exa-cel, suspended in a cryopreservative medium.

3.3 Rationale for Development of Exa-cel

The development of exa-cel is grounded in human genetics showing that elevated levels of HbF result in improved morbidity and mortality in patients with SCD. Elevated HbF addresses the underlying cause of SCD by preventing HbS from inducing RBC sickling, which is the proximate cause of disease manifestations.[27]

The protection garnered from elevated HbF in patients with SCD are demonstrated in 2 examples from natural history, neonates/infants with SCD and SCD-HPFH individuals.

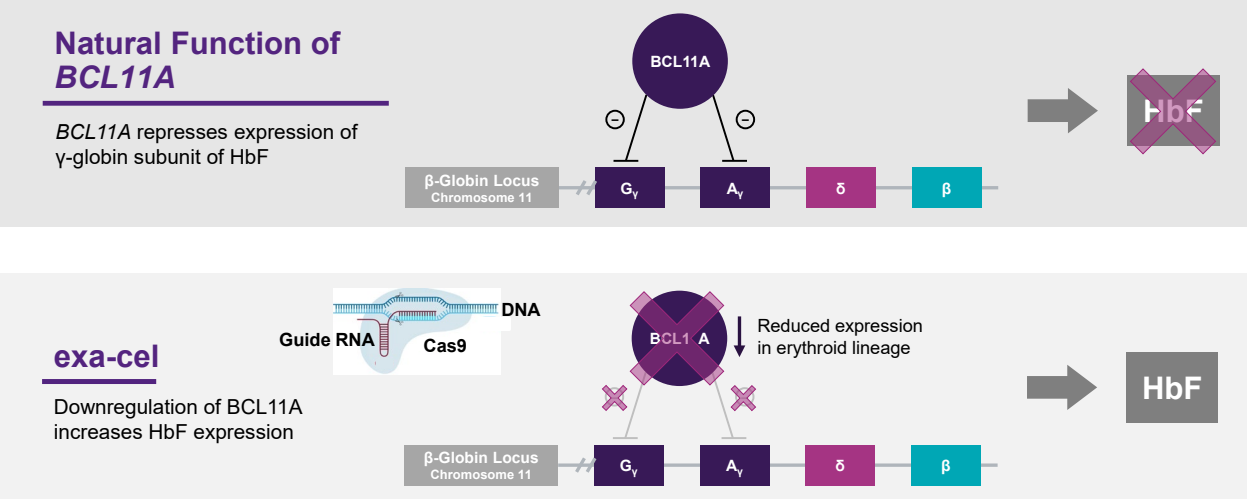
- Neonates and infants with SCD are typically asymptomatic while their HbF levels remain high and become symptomatic during the first year after birth when the synthesis of HbF declines.[58]
- Elevated HbF (%) levels ≥ 20% are known to be protective against disease complications, including preventing VOCs, as in individuals with SCD who coinherit HPFH (SCD-HPFH). Individuals with SCD-HPFH with levels ≥ 20% and higher are generally healthy and have few if any disease complications. [14, 27, 28, 31]

3.4 Mechanism of Action

Exa-cel is a nonviral system that uses CRISPR/Cas9 gene editing to specifically downregulate expression of BCL11A in erythroid progenitors of the bone marrow to reactivate production of endogenous HbF. The mechanism of action (MOA) of exa-cel treatment results in reactivation of HbF production to levels known to eliminate disease complications (HbF ≥20%).[14, 27, 28, 59] The genomic target edited by CRISPR/Cas9 in exa-cel is an intronic erythroid specific enhancer of the *BCL11A* gene that is optimal for the following reasons. First, the erythroid specific enhancer was identified by human genetics as carrying naturally occurring genetic variation that raises HbF levels, mitigates clinical severity of SCD, and has no other clinical consequences. Second, the intronic location means that the target is non-coding, > 25kb from any protein coding sequence, and thus on-target gene edits have no potential impact on function of the encoded BCL11A protein. Third, the erythroid specific nature of the enhancer dictates that the level of BCL11A protein is lowered only in the erythroid lineage, and thus on target edits have no effect in other hematopoietic cell lineages such as B lymphocytes and HSCs. Fourth, the target sequence is unique in the genome, enabling a highly specific guide RNA that doesn't bind elsewhere where it could cause off-target editing. In summary, the selection of this intronic erythroid specific enhancer is a key element in ensuring the efficacy, precision, and safety profile of exa-cel.

The permanent, irreversible, and precise edit in exa-cel generated by CRISPR/Cas9 is directed by the highly specific guide RNA, SPY101, which targets a critical binding site of the transcription factor GATA1 in the non-coding erythroid lineage-specific enhancer region of the *BCL11A* gene on chromosome 2.[33, 34, 60] Repair of these breaks by nonhomologous end joining produces insertions and deletions (indels) in the DNA that disrupt GATA1 binding, thereby lowering BCL11A transcription in erythroid cells only, preserving the normal function of *BCL11A* in other cell types. The reduction of *BCL11A* gene transcription leads to increases in levels of HbF (Figure 4). Reactivation of HbF via exa-cel treatment is the same, regardless of age, sex, race, or disease genotype.

Figure 4: Mode of Action of *BCL11A* Suppression and Resultant γ-Globin De-Repression



CRISPR=clustered regulatory interspace short palindromic repeats; Cas9=CRISPR-associated 9 nuclease; HbF=fetal hemoglobin.
Note: Modified from Reference [61].

Exa-cel has the following advantages:

1. The approach is precise with a single specific genomic target.
2. The effects are permanent, as there is no known mechanism to revert an edit to wild type nor change the native reactivation of HbF.
3. The MOA results in increases in HbF regardless of age, sex, race, or disease genotype.
4. There is no risk of insertional mutagenesis as the product does not rely on viral vector insertion.[62]
5. As detailed in Section 5, exa-cel has been extensively characterized for off-target editing, and no evidence of off-target editing has been observed.

On-target and potential off-target editing were systematically evaluated using multiple complementary methods[62]; see Section 5. These data show high levels of on-target editing and no evidence of off-target editing down to the level of detection of highly sensitive methods and no evidence of chromosomal translocations.

3.5 Chemistry, Manufacturing, and Controls

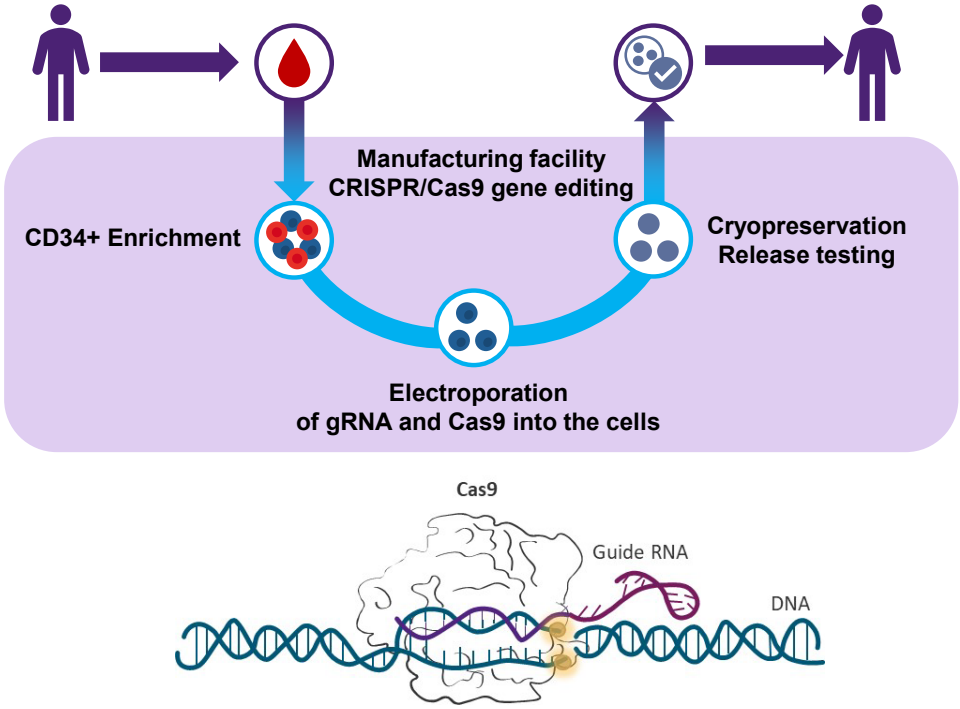
Exa-cel drug product is made with a continuous manufacturing process without an isolated drug substance. The drug product formulation has remained unchanged throughout development. In addition, the same or equivalent manufacturing equipment and controls have been used throughout development and clinical manufacturing. Finally, the manufacturing process has

remained the same, with only minor changes and step optimizations throughout clinical development. The manufacturing steps are:

1. CD34⁺ Enrichment
2. Electroporation
3. Cryopreservation and Release Testing (Figure 5)

Specifically, editing of the CD34⁺ cells occurs following electroporation of a ribonucleoprotein (RNP) complex composed of the Cas9 nuclease and a highly specific guide RNA for the intronic erythroid specific enhancer of the BCL11A gene. The *ex-vivo* editing process is transient, so there is no residual gene editing activity in the cells delivered to the patient. The drug product is tested for release for patient dosing via a robust quality system, including specifications for appearance, identity, purity, potency, cell count/viability, and safety. The release tests and specifications ensure that the product will be manufactured consistently over time and with the appropriate quality. The exa-cel drug product shelf life is 24 months.

Figure 5: Overview of Manufacturing Process for Exa-cel Drug Product



exa-cel=exagamglogene autotemcel; Cas9=CRISPR-associated protein-9; CRISPR=clustered regularly interspaced short palindromic repeats.
Note: Manufacturing steps were unchanged throughout development, including CD34⁺ enrichment, electroporation, cryopreservation, and release testing.

4 CLINICAL DEVELOPMENT PROGRAM

Summary

- The overall clinical development program consists of two pivotal Phase 1/2/3 studies and one Phase 3 long-term follow-up study
  - Study 121 evaluated efficacy and safety in patients with SCD ages 12 to 35 years
  - Study 111 evaluated efficacy and safety in patients with TDT ages 12 to 35 years
  - Study 131 continues efficacy and safety evaluations for up to 15 years of total follow-up in all patients from Studies 121 and 111 who received exa-cel infusion
- All studies were designed in consultation with the Agency: 121 and 111 studies have a sample size of approximately 45 patients each and are 2 years in duration.
- Study 121 has completed enrollment and dosing of all planned patients (46 patients)
- 44 patients with SCD had received exa-cel as of the 14 June 2023 data cutoff date, 12 of whom are adolescents between the ages of 12–18 years
- Exa-cel has received Fast Track, Orphan Drug Designation, Regenerative Medicine and Advanced Therapy Designation, Rare Pediatric Disease Designation, and Priority Review for SCD
- During discussions with the Agency, it was agreed that all data would be submitted for review including analysis to support traditional and accelerated approval options.

4.1 Clinical Development Program

Exa-cel was designed as a one-time, potential functional cure for patients with SCD. The development plan included a parallel program to develop exa-cel as a potential functional cure for transfusion-dependent beta-thalassemia (TDT) using the same MOA. Therefore, the overall development program for exa-cel includes 2 pivotal studies: Study 121 in SCD and Study 111 in TDT, and a long-term follow-up study (Study 131 for both indications; Table 5). The BLA for TDT was submitted separately and is currently under review by the Agency.

All studies were designed in consultation with the Agency: 121 and 111 studies have a sample size of approximately 45 participants, with approximately 30% adolescent patients age 12 to <18 years, and are 2 years in duration. The 131 study is the long term follow-up study designed to study patients who roll-over from the 111 and 121 studies and provides a total of up to 15 years of follow-up after exa-cel infusion (Section 4.1 and Table 5).

Study 121 has completed enrollment and dosing of all planned patients (46 patients in total). The clinical data package for SCD includes data from prespecified interim analysis 2 (IA2; data cutoff date 10 February 2023) from Study 121 which was submitted with the initial BLA and included 20 patients in the Primary Efficacy Set (PES). The updated data analysis based on a 14 June 2023 cutoff, was requested by FDA to further assess durability and safety. In this updated data, 30 patients with at least 18 months of follow-up were included in the PES, 6 patients between ages 12 to <18 years, and were available for evaluation of the primary efficacy endpoint (See Section 7.2.11 for details)

Table 5: Overview of Studies in Exa-cel Clinical Development Program

Study (Indication; Status)	Phase and Objective	Population	Design	Duration	Countries with Enrolled Patients
Study 121 (SCD; Ongoing)	Phase 1/2/3, pivotal study to evaluate the efficacy and safety of exa-cel	Patients with severe SCD ages 12-35 years (inclusive) β^S/β^S, β^S/β^0, or β^S/β^+ genotype	Single-arm, single-dose, multi-center	2 years after exa-cel infusion	United States, Canada, United Kingdom, France, Belgium, Germany, and Italy
Study 111 (TDT; Ongoing)	Phase 1/2/3, pivotal study to evaluate efficacy and safety of exa-cel	Patients with TDT ages 12-35 years (inclusive) β^0/β^0 and non-β^0/β^0 genotype	Single-arm, single-dose, multi-center	2 years after exa-cel infusion	United States, Canada, United Kingdom, Germany, and Italy
Study 131 (SCD+TDT; Ongoing)	Phase 3, long-term follow-up to evaluate long-term safety and efficacy of exa-cel	Patients with TDT or SCD who received exa-cel in Studies 111 or 121	Long-term follow-up	Total follow-up of 15 years after exa-cel infusion	United States, Canada, United Kingdom, Germany, and Italy

Exa-cel=exagamglogene autotemcel; SCD=sickle cell disease; TDT=transfusion-dependent β-thalassemia.

Two additional studies in pediatric patients ages 2 to 11 years are ongoing (Study 151 in children with SCD and Study 141 in children with TDT).

4.2 Regulatory History

IND 018143 was opened with the Office of Tissues and Advanced Therapies by CRISPR Therapeutics on 10 October 2018 for the treatment of SCD and TDT. On 30 November 2018, the IND was transferred to Vertex Pharmaceuticals Incorporated (Sponsor).

In the US, exa-cel has been granted Fast Track, Orphan Drug Designation, Regenerative Medicine Advanced Therapy (RMAT) Designation, Rare Pediatric Disease Designation, and Priority Review for treatment of SCD.

Throughout the clinical program, the Sponsor has engaged with FDA for alignment on many key elements, including trial design, sample size, definitions of clinically meaningful endpoints, and statistical analysis plans.

4.3 Basis for Traditional and Accelerated Approval

During discussions with the Agency, it was agreed that all data would be submitted for review including analysis to support traditional and accelerated approval options. The data for traditional approval is based on the primary endpoint of absence of any severe VOC (i.e., VOC free) for at least 12 consecutive months (VF12); after exa-cel infusion 29 of 30 (97%) patients

achieved VF12 with at least 18 months follow-up and is supported by the key secondary and exploratory endpoints.

The data for accelerated approval is based on the surrogate efficacy biomarker of HbF (%) ≥ 20% at 6 months and the intermediate clinical endpoint (ICE) of absence of severe VOC i.e., VOC free) for at least 9 consecutive months (VF9) as reasonably likely to predict clinical benefit of VF12. Epidemiology and real-world evidence data support that elevated HbF (%) ≥ 20% is predictive of clinical benefit, specifically in avoiding VOC.[27, 28, 32] Real-world evidence studies (using Medicaid data and CIBMTR data[41]) from patients with SCD after allo-HSCT support that VF9 is predictive of VF12. In the 121 study, 40 of 40 (100%) patients met the surrogate biomarker endpoint of HbF (%) ≥ 20% at 6 months, including 11 of 11 (100%) adolescents and 31 of 32 (97%) patients met the endpoint of VF9, including 7 of 7 (100%) adolescents. Per FDA guidance, if a drug is approved via an accelerated pathway, the Sponsor should complete a confirmatory trial to verify the clinical benefit. For exa-cel this requirement for the completion of a confirmatory trial can be met by completion of Study 121 which is fully enrolled and has dosed all patients. Final data for Study 121, which follows patients for a two-year period, will be available the second half of 2025.

5 SUMMARY OF NONCLINICAL ASSESSMENTS

- High rates of allelic editing at the on-target site (~80%) were observed *in vitro* during analyses of exa-cel in CD34$^+$ HSPCs, with 76% of clones carrying biallelic edits.
- On-target editing increased γ-globin mRNA expression and HbF protein expression which were similar in CD34$^+$ HSPC's from both healthy donors and patients with SCD.
- No adverse findings or tumorigenicity were observed *in-vivo* after engraftment of exa-cel in NSG mice at doses up to 11-fold higher than those assessed in human studies.
- Biodistribution of human CD45$^+$ cells in non-hematopoietic tissues (brain, heart, jejunum, mammary gland, ovary, pancreas, prostate, skeletal muscle, testis, and uterus) following engraftment of exa-cel in NSG mice was low and the same as mice engrafted with unedited cells.
- Editing rates were maintained over 16 weeks following transplant with exa-cel in NSG mice, indicating successful editing of the long-term HSCs. Levels of engraftment *in vivo* was indistinguishable between exa-cel and unedited cells.
- No evidence for induction of the innate immune response was seen when CD34$^+$ cells were genetically modified with CRISPR/Cas9
- Extensive off-target assessment in CD34$^+$ samples from both healthy donors and SCD patients revealed no detectable off-target edits or evidence of chromosomal abnormalities following treatment with exa-cel.

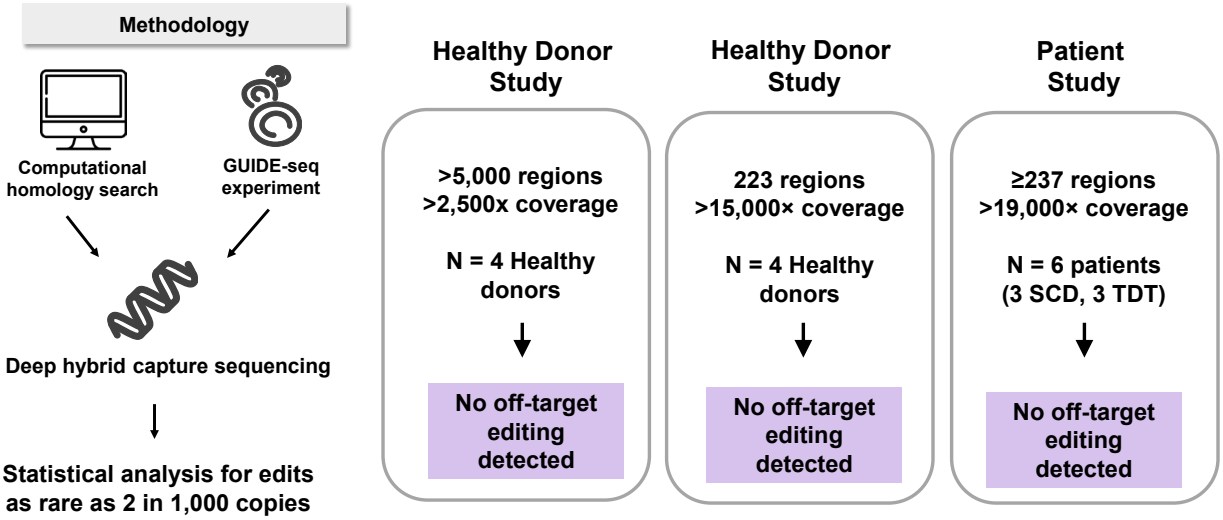
5.1 Overview of Nonclinical Safety and Toxicology Evaluations

In-vitro editing rate at the target *BCL11A* erythroid specific enhancer and induction of HbF were assessed in SPY101-RNP-edited CD34$^+$ HSPCs from healthy donors and patients with SCD and β-thalassemia. An *in-vivo* nonclinical study was performed to test engraftment of exa-cel in sub-lethally irradiated NOD/SCID/IL2Rγnull (NSG) xenotransplant mice. The NSG mouse model was selected as a relevant animal model for all *in-vivo* studies because human CD34$^+$ HSPCs can engraft, proliferate, and develop in these immunocompromised mice.[63, 64] Moreover, the NSG mouse has been used to support nonclinical studies and registration of cell therapy products with historical background data available. This model was used to evaluate long-term engraftment potential and persistence of editing of exa-cel at 16 and 20-week timepoints. At termination, various hematopoietic lineages derived from exa-cel were tested to evaluate multilineage differentiation *in-vivo*.

Peripheral blood, mobilized with granulocyte colony-stimulating factor (G-CSF) plus plerixafor, derived CD34$^+$ human hematopoietic stem and progenitor cells (hHSPCs) were evaluated as part of process qualification runs. The nonclinical research drug product is considered representative of the clinical product.

To evaluate the potential for off-target editing, an exhaustive off-target editing assessment was performed with three different experiments encompassing 14 individuals including 4 of African ancestry of which 3 were SCD patients (Figure 6). These off-target studies examined sites nominated based on information about human genetic variation in homology searches down to a frequency of 1% in samples of African ancestry from the 1000 Genomes Project.[65] While each experiment showed high rates of editing at the on-target site (as a positive control), no evidence for off target editing was observed in any sample or at any nominated site.

Figure 6: Overview of Off-Target Editing Assessments



N=total sample size

5.1.1 Pharmacology

Editing Efficiency and Induction of HbF among Healthy Donors

SPY101-RNP editing of CD34⁺ hHSPCs in cell lots manufactured by a process consistent with the manufacturing process used in clinical studies showed a mean allele editing frequency of 80% (n=10; SD ± 6%). *In vitro* erythroid differentiation of CD34⁺ hHSPCs derived from healthy donors with normal β-globin levels showed a robust increase in γ-globin mRNA transcript levels with mean γ-globin mRNA frequencies of 29% (SD ± 16%) in SPY101-RNP-edited samples, compared to 9% (SD ± 6%) in unedited controls. Similarly, SPY101-RNP-edited samples showed elevated γ-globin mRNA frequencies of 41% (SD ± 15%) compared to 16% (SD ± 11%) in unedited control CD34⁺ hHSPCs.

An analysis of individual colonies demonstrated that SPY101-RNP-edited indels consistently upregulated γ-globin by introducing indels into the GATA1 transcription factor binding site in the erythroid-specific enhancer region of the *BCL11A* gene (See Section 3.4 for additional details on MOA). Overall, ≥ 90% of colonies had at least one allele containing indels that support exa-cel's MOA of disrupting/deleting the GATA-1 binding site in the erythroid-specific enhancer region of the *BCL11A* gene (See Section 2.3 for additional details on MOA). The majority (76%) of colonies had bi-allelic indels, which corresponds with the highest levels of γ-globin production. Analyses of individual colonies aligned with those of the originating bulk population, as the single cell colonies' most frequent indel species also occurred with the highest frequency in the originating bulk population of CD34⁺ hHSPCs.

Additional genotype analysis was performed to see if there was any difference between specific indel patterns and γ-globin expression. All clones containing bi-allelic indels showed consistent and significant upregulation of γ-globin and HbF as compared to unedited clones suggesting that all indels that disrupt the GATA1 binding site in the erythroid enhancer of *BCL11A* upregulate HbF to the same extent.

In summary, treatment of CD34+ hHSPCs with SPY101-RNP causes efficient editing and increases γ-globin transcription upon erythroid differentiation. Genotype analysis of erythroid colonies derived from SPY101-RNP-edited CD34+ hHSPCs revealed that most colonies contained indels on both alleles of the erythroid lineage-specific enhancer of the *BCL11A* gene. In addition, most indels disrupt the GATA1 binding site sequence within the erythroid enhancer of *BCL11A* intron 2 and are associated with γ-globin upregulation. This is consistent with the expected mechanism of SPY101-RNP mediated de-repression of γ-globin gene expression through GATA1 regulation of *BCL11A* expression. These data demonstrate a correlation between editing frequency and expression of gamma globin mRNA. The dose-dependency is driven by the number of edited alleles. Colonies with bi-allelic edits had significantly higher gamma globin mRNA than those with mono-allelic edits or colonies without edited alleles.

Editing Efficiency and Induction of HbF in Samples from Patients with SCD

High editing frequencies were observed in peripheral blood mononuclear cell (PBMC)-purified CD34+ cells from one patient with SCD and one healthy donor (75% in both). All samples showed upregulation of γ-globin mRNA with SPY101-RNP treatment, which ranged from 20% to 56% in samples from healthy donors and 38% to 65% in samples from patients with SCD. In samples from healthy donors, HbF (%) increased from 25% to 28% in cells edited with SPY101-RNP, as compared to 4% to 8% in the control group. Similarly in samples from patients with SCD, HbF (%), increased from 30% to 48% in samples edited with SPY101-RNP, as compared to 8% to 18% in the control group.

Persistence of Edited Cells

Long-term repopulating HSCs represent a small subset of the overall bulk CD34+ cell population. Nonclinical evaluation of editing of this long-term hematopoietic stem cell (LT-HSC) population was performed by measuring persistence over 16 weeks in transplant studies in NSG mice. Highly efficient editing by SPY101-RNP was observed in bulk CD34+ hHSPCs and the edit persisted through 16 weeks after transplantation with allelic editing rate of 91% (n=44, SD ± 15%) in bone marrow at Week 16. Erythroid differentiation was unchanged following editing with SPY101-RNP and high persistence of on-target editing was seen following erythroid differentiation of cells obtained from the bone marrow of mice 16 weeks post-engraftment.

***In-vivo* Pharmacology**

Exa-cel was evaluated in an engraftment study in NSG mice to assess the long-term and multilineage engraftment potential of the edited cells, as compared to controls; and to demonstrate long-term persistence of the edited cells at 16- or 20-weeks after transplant. Results at both timepoints showed no difference in engraftment chimerism between exa-cel or control-treated CD34+ hHSPCs that went through the same cell manufacturing process. The engrafted cells retained their multi-lineage potential.

5.1.2 Pharmacokinetics

A 20-week GLP biodistribution and persistence study was performed in sub-lethally irradiated NSG mice to assess the potential of CRISPR/Cas9-edited human cells to engraft in target tissues, as well as migrate to, accumulate, and persist in non-target organs. Detection of human

cells (i.e., SPY101-RNP-edited hHSPCs and any progeny) was performed in blood, bone marrow, spleen, brain, heart, injection site (tail), intestine (jejunum), kidney, liver, lung, mammary gland, ovary, pancreas, prostate, skeletal muscle, testis, and uterus.

Following exa-cel infusion of 1×10^6 cells/mouse, engraftment of human cells was confirmed in whole blood, spleen, and bone marrow. Generally, there was no difference observed in engraftment between exa-cel and unedited $CD34^+$ HPSCs. Biodistribution of human $CD45^+$ cells in non-hematopoietic tissues following engraftment of exa-cel in NSG mice was low (< 2.4% in highly vascularized and perfused tissues [liver, lung, kidney], < 0.6% at injection site, and < 0.3% in less-vascularized tissues [brain, heart, jejunum, mammary gland, ovary, pancreas, prostate, skeletal muscle, testis, and uterus]) and indistinguishable from mice injected with unedited $CD34^+$ HSPCs. This is consistent with human tissue resident macrophages and innate lymphoid cells in the humanized mouse model.[66]

5.1.3 Toxicology

Single-Dose Toxicity

Studies in NSG mice yielded a no observed adverse effect level for IV exa-cel of 1×10^6 cells/mouse (approximately 3.33×10^7 cells/kg), which was the only dose tested and is 10-fold higher than the minimum recommended dose for patients ages ≥ 12 years.

Off-Target Analysis

A comprehensive analysis was performed to evaluate whether treatment with exa-cel created any changes to genomic DNA outside of the on-target site at the *BCL11A* intronic erythroid specific enhancer. No evidence for chromosomal abnormalities or off-target editing was found.

No chromosomal translocations or other detectable abnormalities were observed by karyotyping of $CD34^+$ HSPCs following treatment with SPY101-RNP from healthy donors. Long-range PCR and split-read analysis of hybrid capture data at the on-target region indicate the majority of edits introduced by SPY101-RNP are small indels (less than 30 bp), with no evidence to indicate the presence of translocations.

No off-target editing was observed spanning three off-target assessments performed in $CD34^+$ HSPCs from healthy donors and patients. Two of these studies assessed the potential for off-target editing in healthy donors, and one study addressed the potential impact of genetic variation on off-target editing and directly addressed off-target editing in the relevant patient populations. In total these evaluations spanned 14 individuals including 3 patients with SCD and 4 individuals of African descent.

In each off-target assessment, candidate off-target sites were nominated using two orthogonal methods: one based on sequence homology of the guide to any other sites in the human genome, and the second an empirical method unbiased by sequence homology termed GUIDE-Seq.[67] As an internal positive control for each GUIDE-seq experiment, it was required that the on-target site (the *BCL11A* enhancer) was successfully detected, with a high coverage of GUIDE-seq reads (>8,000). All candidate sites nominated by either method were then evaluated in an independent editing experiment using a highly sensitive next-generation sequencing hybrid capture method searching for any off-target change in DNA sequence

between edited and unedited CD34+ HSPCs. Similar to the GUIDE-seq experiment, as a positive control for each hybrid capture experiment, it was required that high and statistically significant editing was observed at the on-target site. Moreover, to ensure sensitivity, high sequencing coverage was obtained across the nominated candidate off-target sites (>2,500x median coverage). The first two experiments studied healthy volunteers. The third experiment evaluated off-target potential in patients with SCD and TDT, and also incorporated knowledge of human genetic variation from the 1000 Genomes Project to nominate additional candidate off-target sites that might be created by inherited genetic variants.[65] (Note that a potential off-target site recently nominated in the literature based on genetic variation[68] was included in all three off-target assessments).

No off-target editing was observed in any individual at any site in any of the three experiments.

Details of the three assessments are as follows:

Assessment 1 studied CD34+ HSPCs from four healthy donors edited with SPY101. Site nomination included (1) a broad homology search that included any site with up to 5 mismatches or up to 2 mismatches and 1 gap relative to the on-target sequence, and (2) GUIDE-Seq performed in 1 healthy donor under multiple experimental conditions. This homology search incorporated any site matching both canonical (NGG) and non-canonical PAMs (NAG, NGA, NAA, NCG, NGC, NTG, NGT). A total of 5,007 homology regions and 857 GUIDE-Seq regions were nominated. Hybrid capture deep sequencing (> 2,500× median coverage) was performed on each candidate regions in four healthy volunteers. Candidate off-target sites were evaluated for an indel frequency difference between edited and unedited samples of ≥ 1.0%.

No off-target editing was observed.

Assessment 2 studied CD34+ HSPCs from four additional healthy donors. This assessment focused on: (1) candidate off-target sites most likely to have off-target editing based on 3 mismatches or up to 2 mismatches and 1 gap relative to the on-target sequence; and (2) additional regions nominated by a second GUIDE-Seq experiment using CD34+ HSPCs from 2 healthy donors under a single, optimized experimental condition. In total, 223 nominated candidate off-target regions were sequenced in four healthy donors using ultra-deep sequencing (> 15,000× median coverage) enabling sensitivity down to an even more stringent difference threshold of ≥ 0.2%.

No off-target editing was observed.

Assessment 3 studied potential for off-target editing in SCD and TDT patients. Edited and unedited CD34+ HSPCs from 6 patients (3 with SCD and 3 with TDT) enrolled in exa-cel clinical studies were evaluated for off-target editing. In addition to (1) the 223 regions evaluated in the second off-target study, additional sites were nominated based on (2) variant-aware homology search for any off-target regions created by inclusion of SNPs from the 1000 Genomes Project, and (3) additional GUIDE-Seq experiments performed in CD34+ HSPCs from each of the 6 patients. The variant-aware homology search identified 9 additional candidate off-target sites where a common SNP (MAF > 10%) would create a site that met our homology criteria (3 mismatches or 2 mismatches and 1 gap, with a PAM of NGG, NGA, NAG, NAA, NCG, NGC,

NTG, NGT). This search used all relevant SNPs from the 1000 Genomes Project database[65], which evaluated individuals with diverse genetic backgrounds, including 661 individuals of African ancestry. Ultra-deep hybrid capture sequencing (>19,000x median coverage) was performed at each of these candidate regions in each of the 6 patients. Genotyping was performed at each variant site for each of the 6 patient samples; at least one patient sample carried the variant allele at each of the 9 variant allele sites. Search for off-target editing was performed with sensitivity to detect editing down to an indel frequency difference threshold of 0.2%.

No off-target editing was observed at any site in any patient sample, including those carrying the variant allele at the nominated variant aware site.

Finally, to assess any potential impact of genetic variation of even lower frequency, we performed a variant-aware homology search using SNPs present at a low frequency (> 1%) in any one of the 5 continental groups from the 1000 Genomes Project (Africa, East Asia, South Asia, Europe, and the Americas). This analysis nominated 41 additional candidate off-target sites. We performed ultra-deep hybrid capture sequencing (> 10,000x median coverage) at each of these 41 candidate regions in 3 patient samples; 1 SCD and 2 TDT. Genotyping was performed at each variant site for each of the 3 patient samples. As expected, given the rare variants in this search, fewer variant alleles were identified for these 41 sites as compared to the 9 sites (above) based on more common variants: for 3 of 41 rare variant aware sites, at least one patient sample carried the variant allele. Search for off-target editing was performed with sensitivity to detect editing down to an indel frequency difference threshold of 0.2%.

No off-target editing was observed at any site in any patient sample, including those carrying the variant allele at the nominated variant aware site.

In summary, across all 3 assessments, no off-target editing was observed at any region in any donor sample.

Carcinogenicity

The toxicity and potential for tumorigenicity was evaluated in a GLP 20-week study in NSG mice. The positive control for tumorigenicity (HL-60 cells) was selected based on a 55-day non-GLP exploratory study.

In the pivotal 20-week GLP combined toxicity and tumorigenicity study, sub-lethally irradiated NSG mice were administered a single dose of any of: 1×10^6 cells/mouse of exa-cel; 1×10^6 cells/mouse of unedited $CD34^+$ hHSPCs; 0.2×10^6 cells/animal of HL-60 (positive control); or vehicle. Engraftment of cells from all donors was confirmed in whole blood, bone marrow and spleen, and no difference in chimerism was observed between edited and unedited cells. Exa-cel was well tolerated, and there were no exa-cel-related deaths, clinical signs, effects on clinical chemistry parameters, or blood and bone marrow smears, or macroscopic observations. After a 20-week follow-up period, no neoplasms were identified in mice that received either exa-cel or unedited $CD34^+$ hHSPCs.

Immunogenicity

A nonclinical study was conducted in $CD34^+$ hHSPC to determine whether electroporation with SPY101-RNP leads to an innate immune response and cell death *in vitro*. Results showed that cell viability was > 80% for all treatment groups at all timepoints, with a slight decrease in viability at 48 hours with SPY101-RNP treated $CD34^+$ cells, relative to other groups. Compared to untreated $CD34^+$ cells, treatment of $CD34^+$ cells with SPY101-RNP did not result in increased expression of genes that would indicate a type-1 interferon (IFN) response. Treatment of PBMCs with the IFN-inducing positive control (resiquimod [R-848]) significantly increased expression of all genes that would indicate a type-1 IFN response; however, it did not increase gene expression in $CD34^+$ cells.

5.2 Conclusions from Nonclinical Assessments

Results from the nonclinical pharmacology, biodistribution, and toxicology studies support approval of exa-cel as a treatment for patients ages ≥ 12 years with SCD. Nonclinical assessments support clinical findings, demonstrating that exa-cel has:

- No evidence of chromosomal abnormalities or translocations.
- No evidence for off-target editing.
- Low risk for inducing an innate immune response during *ex-vivo* editing.
- Resulted in no adverse findings, tumorigenicity, or unwanted biodistribution to non-target tissues in NSG mice at a higher dose than was assessed in human clinical trials.

6 OVERVIEW OF CLINICAL PHARMACOLOGY

Summary

- Busulfan pharmacokinetics were sufficient to allow engraftment of exa-cel with a targeted cAUC of 74 mg·h/L to 90 mg·h/L following once daily dosing or 59 mg·h/L to 89 mg·h/L following every 6-hour dosing
  - Safety of busulfan myeloablative conditioning was consistent with its known safety profile
  - Patient demographics and medical characteristics did not alter busulfan's effects
- Exa-cel doses in humans have ranged from 2.9 to 14.4 × 10^6 cells/kg with successful engraftment and well tolerated safety profile
  - The minimum recommended dose is 3.0 ×10^6 cells/kg with no maximum dose identified
  - Literature supports no maximum dose for $CD34^+$ transplantation and a standard practice to infuse all $CD34^+$ cells available
- Allelic editing was high and stable
- Fetal hemoglobin, measured in both g/dL and as a percentage of total Hb (HbF [%]) were maintained at levels known to be protective against disease in both SCD and TDT
- There were no identified or expected effects either from intrinsic factors, such as age, sex, race, or genotype, or from extrinsic factors

Standard approaches to characterize drug dose, PK, and pharmacodynamics, including dose-ranging, mass balance, and drug-drug interaction studies, do not apply to cell and gene therapies in the same manner as for small molecule therapies. Instead, the proportion of alleles with the intended genetic modification (allelic editing) in the peripheral blood and in the $CD34^+$ cells of the bone marrow was assessed to evaluate persistence of the edited cells. Other efficacy endpoints (e.g., HbF [%]) indicative of the pharmacology resulting from successful delivery and engraftment of the edited LT-HSCs were evaluated. These parameters are discussed in the context of exa-cel efficacy in Section 7.

Myeloablation is a required step before exa-cel infusion in order to deplete endogenous HSCs from the patient's bone marrow and allow hematopoietic repopulation with gene-edited LT-HSCs. Busulfan was used as a single agent for myeloablative bone marrow conditioning in Study 121.

Busulfan's effectiveness in myeloablation is dependent on cumulative exposure (cumulative area under the concentration versus time curve [cAUC]) over 4 days of dosing. Patient doses were adjusted based on PK monitoring with the aim of meeting target busulfan AUC levels per guidance provided in the protocol. Administered busulfan regimens and cumulative exposures were evaluated for correlations with key treatment milestones, such as neutrophil and platelet engraftment, and are discussed in Section 6.1. No clinically relevant relationship was observed between individual patient time to neutrophil or platelet engraftment and observed busulfan cAUC or busulfan dose regimen.

6.1 Busulfan Pharmacokinetics

Pharmacokinetically adjusted single-agent busulfan was used for myeloablation in Study 121, with a targeted cAUC of 74 mg·h/L to 90 mg·h/L following once daily dosing or 59 mg·h/L to

89 mg·h/L following every 6-hour dosing. The latest analysis performed on PK of busulfan was performed at IA2 (N=42). These results are summarized below. A total of 44 patients have received busulfan conditioning, with two after the IA2 data cut-off date. These two additional patients had PK parameters similar to results from IA2 and were within the protocol-specified target range.

At the time of IA2, a total of 42 patients underwent busulfan conditioning with either once daily (qd) or every 6 hours (q6h) regimens. Patient demographics and medical characteristics did not alter busulfan's effects. Myeloablation, as performed in this study, was adequate and sufficient because all patients with sufficient follow-up (at least 44 days) after exa-cel infusion achieved profound neutropenia and achieved engraftment of edited cells, with stable allelic editing over time.

6.2 Exa-cel Dose Rationale

The clinical data supports the selection of the minimum dose of 3.0×10^6 $CD34^+$ cells/kg. A total of 44 patients have received doses of exa-cel ranging from 2.9 to 14.4×10^6 $CD34^+$ cells/kg (median of 4.0×10^6 $CD34^+$ cells/kg). All administered doses led to successful neutrophil engraftment, and no patients received rescue backup cells (Section 8.4). All doses studied were well tolerated with a favorable safety profile that was generally consistent with the risks of myeloablative busulfan conditioning and HSCT (Section 8). Also, patients with sufficient follow-up time had increases in HbF (%) from baseline and the results for the primary and key secondary endpoints were statistically significant and clinically meaningful (Section 7.2).

A maximum dose is not proposed for exa-cel. The dose of $CD34^+$ cells is constrained only by the number of cells collected from the patient and subsequently edited. This is consistent with the autologous HSCT literature, in which there is no maximum $CD34^+$ dose described, and with standard clinical practice to infuse all $CD34^+$ cells available.

In summary, the recommended minimum dose of 3.0×10^6 $CD34^+$ cells/kg has been shown to result in a favorable benefit-risk in patients with SCD.

6.3 Persistence of Edited Cells

The proportion of alleles with the intended genetic modification (allelic editing) in the bone marrow and in peripheral blood was assessed to evaluate persistence of the edited cells. As expected, based on the permanent and irreversible edit, stable and durable allelic editing was observed in the bone marrow and peripheral blood. Stability of allelic editing in the bone marrow and peripheral blood over time indicates successful and durable engraftment of edited LT-HSCs. These results are discussed in Section 7.2.7.

6.4 Pharmacodynamics: HbF (%) and F-cell (%)

Consistent with the MOA of exa-cel, HbF (%) and circulating RBCs expressing detectable levels of HbF(F-cell) (%) levels were observed to increase early after exa-cel treatment and were sustained over time. These results are discussed in Section 7.2.6.

6.5 Intrinsic Factors

Subgroup analyses were performed by age at screening, sex, race, and genotype for the following secondary efficacy endpoints: HbF and total Hb, F-cells (%), and allelic editing in peripheral blood and in $CD34^+$ cells of bone marrow.

Overall, results in all subgroups analyzed (age, sex, race, and genotype) were consistent with each other and with results from the main analyses of these secondary efficacy endpoints (Section 7.2.11), indicating that the exa-cel MOA works independently of these factors and weight-based dosing is appropriate to provide clinically meaningful HbF (%) that leads to clinical benefit (absence of VOCs). Therefore, dose adjustment of exa-cel is not needed for any of the evaluated intrinsic factors.

6.6 Extrinsic Factors

No drug-drug interaction studies were performed with exa-cel. Drug-drug interactions are not anticipated with exa-cel, as it does not affect human physiological processes that can in turn alter the PK profiles of co-administered medications. Exa-cel is not expected to interact with the CYP P450 enzymes or drug transporters.

7 CLINICAL EFFICACY IN SICKLE CELL DISEASE

Summary

- All patients who received exa-cel received substantial clinical benefit. The study met the primary and both key secondary endpoints.
- The pivotal Study 121 and long-term follow-up Study 131 showed transformational clinical benefit in adults and adolescents:
  - 29 of 30 (96.7%) patients in the PES achieved VF12, including 6 adolescent patients;
  - 30 of 30 (100%) patients in the PES achieved HF12, including 6 adolescent patients;
  - 40 of 40 (100%) patients achieved the surrogate efficacy biomarker of HbF ≥ 20% at Month 6, including 11 adolescent patients;
  - 31 of 32 (97%) patients achieved the intermediate clinical endpoint (ICE), VF9 including 7 adolescent patients.
- Adolescents (ages 12 to 17 years) comprised ~30% of the total population (n=11). Transformational clinical benefit was consistent between adolescents and adults:
  - Patients achieved rapid, robust, and durable levels of HbF that exceeded the 20% level known from natural history studies to be protective against disease complications, including avoidance of VOCs
  - Allelic editing in the bone marrow and peripheral blood was stable, consistent with the durable engraftment of edited long-term hematopoietic stem cells (LT-HSCs) and reflect the permanent nature of the intended edit
  - HbF levels ≥ 20% at Month 6 is a surrogate efficacy biomarker, and VF9 is an intermediate clinical endpoint that is supportive of accelerated approval
- Markers of hemolysis improved: Mean LDH levels normalized by Month 9 and haptoglobin levels were detectable after Month 6
- Clinically meaningful improvements in Patient Reported Outcomes were observed across all instruments and domains, including those related to pain, general health, physical, emotional, social, and functional well-being.

7.1 Study Designs in Sickle Cell Disease (Studies 121 and 131)

The evidence of exa-cel efficacy in SCD is provided from the pivotal Phase 1/2/3 Study 121 and long-term follow-up Study 131 (See Sections 7.1.1 and 7.1.2 for overviews of respective study designs).

7.1.1 Study 121 Design

Study 121 is a pivotal, single-arm, open-label, global Phase 1/2/3 study for patients ages 12 to 35 years who have SCD with recurrent VOCs. This study evaluates efficacy and safety for 2 years after exa-cel infusion.

An open-label, single-arm study was chosen because of the need for mobilization, apheresis, myeloablation, and subsequent transplant procedures, all of which would be unethical to perform as sham procedures in a control group. Additionally, a concurrent allogenic HSCT control group was deemed inappropriate because allo-HSCT requires different conditioning agents as well as immunosuppressive treatments for prophylaxis and/or treatment for GVHD and graft rejection, which are potential complications of allo-HSCT, but are not risks for exa-cel

treatment. To ensure study integrity and minimize potential operational bias, key trial data including the primary and key secondary endpoints, as well as hematologic endpoints (total Hb, HbF, and allelic editing) were restricted.

A 2-year follow-up was selected because patients were expected to receive RBC transfusions for SCD management and/or post-transplant support after exa-cel infusion for 2 months or longer, as a bridge between transplantation and engraftment. After supportive transfusions, patients transition into the efficacy evaluable period, which starts 60 days after the last RBC transfusion for post-transplant support or SCD management (i.e., a 60 -day RBC washout period). Therefore, Study 121 was designed to afford patients sufficient time to complete the RBC transfusions and 60-day RBC washout period, in addition to being evaluated for the primary and key secondary efficacy endpoints.

7.1.1.1 Study Stages

Study 121 was conducted in 4 stages (Figure 7):

Stage 1 included screening and the premobilization period. During this stage, prophylactic RBC exchange or simple transfusions were recommended for a minimum of 8 weeks before the planned start of mobilization and conditioning regimen, to maintain HbS < 30% to minimize SCD-related complications or VOCs during mobilization/apheresis and peri-transplant in accordance with recommended HSCT and gene therapy protocols for these patients.[69-71]

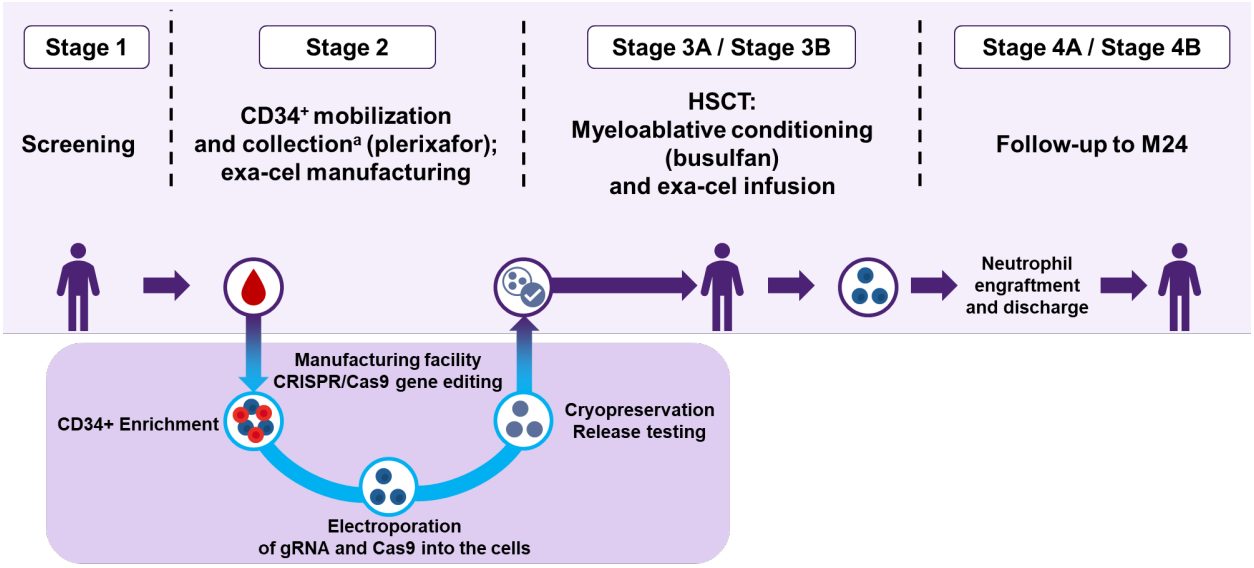
Stage 2 included mobilization, autologous $CD34^+$ cell collection, exa-cel manufacture and disposition. During Stage 2, patients underwent apheresis for up to 3 consecutive days per cycle to collect $CD34^+$ HSPCs.[62, 72-75] (Table 6).

Mobilization of bone marrow $CD34^+$ HSPCs into the peripheral blood for patients with SCD was performed using plerixafor only. Per protocol, if the minimum cell dose and backup was not met, additional mobilization and apheresis cycles could be conducted based on the overall benefit/risk profile for the patient, in discussion with the medical monitor and investigator.

Stage 3 included myeloablative conditioning (Stage 3a; Table 6) and exa-cel infusion (Stage 3B; Table 6). PK-adjusted single-agent busulfan myeloablative conditioning was used, as in other HSC based gene therapy practice for SCD. [72, 73]

Stage 4 included post-infusion in-hospital follow-up (until neutrophil engraftment; Stage 4A) and post-discharge follow-up for up to approximately 2 years after exa-cel infusion (Stage 4B).

Figure 7: Study Design for Study 121



CRISPR/Cas9=clustered regularly interspaced short palindromic repeats and CRISPR-associated nuclease 9; exa-cel=exagamglogene autotemcel; gRNA=guide RNA; Hb=hemoglobin; HbS=sickle hemoglobin; HSCT=hematopoietic stem cell transplantation; M=month; RBC=red blood cell
Notes: Starting at least 8 weeks before first day of mobilization in Stage 2, patients received RBC transfusions to maintain HbS level of < 30% of total Hb while keeping total Hb concentrations ≤ 11 g/dL from Stage 1 through the start of busulfan conditioning in Stage 3A.
a. Includes collection of $CD34^+$ cells as back-up for rescue therapy in the event of non-neutrophil engraftment with exa-cel.

Table 6: Dosing and Administration of Study Drugs, Including Apheresis, Myeloablative Conditioning, and Exa-cel Infusion in Study 121

Study Stage	Description for Study 121
Stage 2: Mobilization and autologous CD34+ stem cell collection	• $CD34^+$ cell mobilization with plerixafor • Plerixafor[a] administered subcutaneously at 0.24 mg/kg approximately 2 to 3 hours before apheresis
Stage 3a: Myeloablative conditioning	• Busulfan administered intravenously: ○ 3.2 mg/kg/day qd for 4 consecutive days OR ○ 0.8 mg/kg q6h for 4 consecutive days ○ Dose adjustment based on PK of the first dose
Stage 3b: Exa-cel infusion	Exa-cel administered via infusion through central venous catheter: • Minimum dose of 3×10^6 $CD34^+$ cells/kg

exa-cel=exagamglogene autotemcel; G-CSF=granulocyte colony-stimulating factor; PK=pharmacokinetics; q6h=every 6 hours; qd=once daily; SCD=sickle cell disease; VOC=vaso-occlusive crisis.
a. Plerixafor alone was used because the administration of G-CSF for mobilization has been shown to induce VOCs in patients with SCD, which can be fatal.

7.1.1.2 Key Enrolment Criteria

7.1.1.2.1 Key Inclusion Criteria

Severe SCD (Patients with Recurrent VOCs)

Severe SCD was defined by the occurrence of at least 2 of the following VOC events per year during the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan, HU):

- Acute pain event that required a visit to a medical facility and administration of pain medications (opioids or IV non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
- Acute chest syndrome (ACS), as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
- Priapism lasting > 2 hours and requiring a visit to a medical facility
- Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥ 2 g/dL.

Criteria similar to the severe VOC criteria listed above, such as recurrent acute pain VOC (≥ 2/year for several years) or recurrent priapism requiring healthcare utilization, or ACS with recurrent hospitalizations while receiving appropriate supportive care and HU are among the disease severity criteria used when considering allo-HSCT for patients with SCD. [76] The most common of these are recurrent episodes of pain exacerbation requiring healthcare utilization.[18, 76]

An independent Endpoint Adjudication Committee (EAC) adjudicated each individual historical VOC (during the 2 years prior to screening) to ensure that the events met the study's severe VOC definition. FDA concurred that this approach defined a broad, inclusive, and objective VOC definition, which captures all VOC events.

Genotype

Patients with SCD with all genotypes can have recurrent VOCs and be severely affected by their disease.[77] The key underlying pathophysiology, production of HbS that triggers VOC events, is identical across genotypes. Therefore, Study 121 enrolled patients with genotypes (β^S/β^S, β^S/β^0, or β^S/β^+) representative of a severe SCD population. Based on the MOA of exa-cel, which reactivates HbF production, it is expected that exa-cel treatment will lead to the prevention of VOC in all SCD genotypes.

Age

Patients aged 12–35 years were included in Study 121, and Sponsor has an ongoing study in patients aged 2-11 years. The upper age limit of subjects in Study 121 was 35 years due to the increased age related risks of busulfan myeloablation in older SCD patients who have accumulated disease related end-organ damage. However, there is no universal upper age limit that defines fitness for busulfan myeloablative conditioning in SCD patients; it is patient specific based on individual characteristics and benefit/risk and thus study results can be extrapolated to older age patients. SCD has the same pathophysiology independent of age, with the same

mutation resulting in production of HbS that triggers VOC events. In addition, the protective effect of HbF against disease complications, including avoidance of VOC, is the same regardless of age and the MOA of exa-cel in reactivating HbF is the same across ages as well. Importantly, treating the disease early will likely provide even greater benefit in adolescents and young children, as they have better tolerability of study procedures, including myeloablative conditioning and transplantation, and treating these patients early may help to preserve end-organ function.[19, 55, 78, 79]

In Study 121, adolescent patients (ages 12 to <18 years) were enrolled and treated once efficacy and safety had been shown in adults (ages 18 to 35 years). In total, 12 adolescent patients have a median follow-up duration after exa-cel infusion of 16.7 months, with the longest follow-up duration in the adolescent age group being 20.6 months. Study 151, in patients with SCD ages 2 to 11 years, is underway and is currently enrolling and dosing.

Hematopoietic Stem Cell Transplant Eligibility

Transplant eligibility was confirmed according to standard practice. The adequate physical function of the patients was confirmed to minimize complications during myeloablative conditioning and transplantation. Therefore, patients ages ≥ 16 years were required to have Karnofsky performance status of ≥ 80%; patients ages <16 years were required to have Lansky performance status of ≥ 80%. All patients were required to have adequate lung, heart, and kidney function. These were defined as: lung, diffusing capacity of the lung for carbon monoxide (DLco) ≥ 50% (corrected for Hb and/or alveolar volume); heart, left ventricular ejection fraction (LVEF) ≥ 45%; and kidney, estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2.

7.1.1.2.2 Key Exclusion Criteria

Patients with any of the following were excluded from study participation:

Insufficient liver function

Because busulfan is metabolized primarily through the liver, patients with advanced liver disease were excluded from the study. Patients were excluded if they had evidence of advanced liver disease as defined by any of: alanine transaminase (ALT) > 3 × the upper limit of normal (ULN); direct bilirubin value > 2.5 × ULN; Baseline prothrombin time (international normalized ratio [INR]) > 1.5 × ULN; a history of cirrhosis; evidence of bridging fibrosis; or active hepatitis.

Patients With Significant Chronic Pain

In addition to VOCs, patients with SCD may also experience chronic pain. Chronic pain may be the result of end-organ damage, such as avascular necrosis (AVN). Chronic pain may also relate to other mechanisms reflecting chronic, non-VOC effects of SCD, such as neuropathic pain and hyperalgesia syndromes resulting from chronic changes in central and peripheral pain pathways.[80] Patients with SCD may also experience acute exacerbations of chronic pain, particularly in context of AVN or as a consequence of chronic pain medication adjustments.[80] Given the potential confounding effect of chronic pain on the assessment of severe VOCs, patients with more than 10 unplanned hospitalizations or emergency department visits related to

SCD in the 1 year before screening that, in the opinion of the investigator, are consistent with significant chronic pain, rather than acute vaso-occlusive pain crises, were excluded.

Patients Unable to Suspend Chronic Transfusions

Patients who were treated with regular RBC transfusions that, in the opinion of the investigator, could not be interrupted after engraftment were excluded because ongoing transfusions could potentially confound measurement and evaluation of the effect of exa-cel on HbF level and other efficacy measures.

Abnormal TCD in Patients 12 to 18 Years Old

An abnormal transcranial Doppler (TCD) velocity (time-averaged mean of the maximum velocity [TAMMV] ≥ 170 cm/sec for non-imaging TCD and ≥ 155 cm/sec for imaging TCD) in specific cerebral arterial segments in children and adolescents aged 12 to 16 years with SCD indicates a high risk of stroke and is an indication for chronic transfusion programs as primary stroke prevention.[81, 82] Patients ages 12–16 years with abnormal TCD at screening or patients ages 12–18 years with a history of abnormal TCD (TAMMV ≥ 200 cm/sec for non-imaging TCD and ≥ 185 cm/sec for imaging TCD) were excluded prior to the benefit-risk of exa-cel being known.

Pregnancy or Breastfeeding

Patients who were pregnant or lactating were excluded from the study in accordance with the busulfan and plerixafor prescribing information.[83, 84]

7.1.1.3 Endpoint Definitions

Prespecified endpoints for Study 121 included the following:

VOC-Related Endpoints

An independent Endpoint Adjudication Committee (EAC) adjudicated each individual historical VOC (during the 2 years prior to screening) and each on-study VOC to ensure that the events met the study's severe VOC definition. The EAC was composed of an independent, external group of experts with appropriate clinical and scientific background to evaluate VOCs. Investigators submitted all available medical records for each individual event to the EAC for review and adjudication.

Additionally, all pain-related events and other experiences that could potentially be interpreted as a VOC were identified and evaluated by the Sponsor. Based on careful review of each event and investigator input, the Sponsor concluded that the EAC received and reviewed all events that could potentially meet the protocol definition of a VOC and no events were missed.

- **Primary Endpoint (VF12)**: Proportion of patients who have not experienced any severe VOC for at least 12 consecutive months after exa-cel infusion. The evaluation of VF12 starts 60 days after last RBC transfusion for post-transplant support or SCD management. Patients evaluable for the primary efficacy endpoint had at least 16 months of follow-up.

- **Second Key Secondary Endpoint (VF9)**: Proportion of patients who have not experienced any severe VOC for at least 9 consecutive months any time after exa-cel infusion. The evaluation of VF9 starts 60 days after last RBC transfusion for post-transplant support or SCD management for patients who reach at least 12 months of follow-up.
- **Secondary Endpoint**: Duration of severe VOC-free in patients who achieved VF12 (the primary endpoint)

A severe VOC is defined as any one of the following events:

- Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions
- ACS, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
- Priapism lasting >2 hours and requiring a visit to a medical facility
- Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥ 2 g/dL

Hospitalization-Related Endpoints

- **First Key Secondary Endpoint (HF12)**: Proportion of patients free from inpatient hospitalization for severe VOCs sustained for at least 12 months after exa-cel infusion. The evaluation of HF12 starts 60 days after the last RBC transfusion for post-transplant support or SCD management. Patients evaluable for HF12 had at least 16 months of follow-up.

Hematologic Parameters (All Secondary)

- Proportion of patients with sustained HbF ≥ 20% at the time of analysis for at least 3 months, 6 months, or 12 months. The evaluation starts 60 days after the last RBC transfusion for post-transplant support or SCD management
- HbF concentrations (in absolute value and %) over time
- Total Hb concentration over time
- Reductions from baseline in the number of annualized RBC Transfusions
- Change in proportion of F-cells over time (**exploratory endpoint**)

Evidence of Allelic Editing (All Secondary)

- Proportion of alleles with intended genetic modification present in peripheral blood leukocytes over time
- Proportion of alleles with intended genetic modification present in $CD34^+$ cells of the bone marrow over time

Markers of Hemolysis (All Secondary)

- Change from baseline in haptoglobin over time
- Change from baseline in lactate dehydrogenase (LDH) over time

Patient-Reported Outcomes (All Secondary)

- Change in patient-reported outcomes (PROs) over time in adults (ages ≥ 18 years) using
    - Pain-scale: 11-point numeric rating scale (NRS)
    - Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT)
    - ASCQ-Me
    - EuroQol Questionnaire-5 dimensions-5 levels of severity (EQ-5D-5L)
- Change in PROs over time in adolescents (12 to <18 years of age) using
    - Pain-scale: 11-point NRS
    - Pediatric Quality of Life Inventory (PedsQL; teen self-report and parent proxy versions)
    - PedsQL SCD module (teen self-report and parent proxy versions)
    - EuroQol Questionnaire – 5 dimensions – 5 levels of severity – youth version (EQ-5D-Y) self-report and parent proxy version

7.1.1.4 Statistical Analysis Plan

7.1.1.4.1 Sample Size Justification

With a sample size of 45 patients planned to receive exa-cel, 3 IA could be performed following a group sequential testing procedure in the study to allow for early evaluation of efficacy. This sample size provided ≥ 95% power to rule out a response rate of 50% when the true response rate is 80% for both the primary and key secondary efficacy endpoints with one-sided alpha of 0.025.

Response rate of 50% was selected because the 3-year event-free survival in patients who do not have a matched related donor and could only receive haplo- or matched unrelated donor transplant is approximately 50%.[20, 22] Additionally, there is a < 10% probability that a patient with ≥ 2 VOC events per year in each of the 2 years before treatment would have a spontaneous VOC elimination in a 12-month period, based on data from the Harvard University/Brigham and Women's Hospital natural history study of 5,874 patients with SCD.[30, 85]

7.1.1.4.2 Analysis Sets

Endpoints in Study 121 were assessed in one of three analysis sets: PES, Early Efficacy Set (EES), and Full Analysis Set (FAS). Table 7 presents the analysis set(s) assessed for each endpoint.

Table 7: Summary of Efficacy Endpoints and Analysis Sets in Study 121

Endpoint Category	Endpoint Definition	Analysis Set(s)
Alpha-controlled endpoints[a]		
Primary	VF12: Proportion of patients who have not experienced any severe VOC for at least 12 consecutive months after exa-cel infusion	PES
First key secondary	HF12: Proportion of patients free from inpatient hospitalization for severe VOCs sustained for at least 12 months after exa-cel infusion	
Second key secondary	VF9: Proportion of patients who have not experiences any severe VOC for at least 9 consecutive months after exa-cel infusion (intermediate clinical endpoint)	EES
Secondary Non-alpha controlled endpoints		
Secondary	• HbF levels over time, including HbF (%) at Month 6 (surrogate efficacy biomarker) • Total hemoglobin concentration over time • Allelic editing • Duration of severe VOC free period • Reduction in RBC Transfusions	FAS PES
	• Markers of hemolysis • Patient-reported outcomes	PES
Exploratory	F-cells over time	FAS PES

EES=Early Efficacy Set; FAS=Full Analysis Set; F-cells= circulating RBCs expressing detectable levels of HbF; Hb=hemoglobin; HbF=fetal hemoglobin; IA=interim analysis; PES=Primary Analysis Set; RBC=red blood cell; VOC=vaso-occlusive event.
Note: Primary and key secondary endpoints were assessed hierarchically as follows: VF12 (primary endpoint), HF12 (first key secondary endpoint), VF9 (second key secondary endpoint).
a. Primary and both key secondary endpoints were alpha controlled for type-1 error and determined as statistically significant at IA2. Results presented are from data cutoff date of 14 June 2023, which was not prespecified and therefore not alpha controlled.

Study 121 included three analysis sets:

- **FAS** includes all patients who received exa-cel infusion. The analyses of patients in this set included data through the end of Study 121. Safety assessments were performed on the FAS.
- **PES** is subset of the FAS and includes subjects who had been followed for at least 16 months after exa-cel infusion. The evaluation of VF12 started 60 days after the last RBC transfusion for post-transplant support or SCD management. Subjects who had less than 16 months follow-up due to death or discontinuation due to adverse events related to exa-cel were also included in this set.
- **EES** was used for the evaluation of VF9 as an intermediate clinical endpoint (Section 7.1.1.3) and was defined as a subset of FAS that includes all patients who have been followed for at least 12 months after exa-cel infusion. The evaluation of VF9 started 60 days after the last RBC transfusion for post-transplant support or SCD management. Subjects who had less than 12 months of follow-up due to death or discontinuation due to adverse events related to exa-cel were also included in this set.

To evaluate long-term efficacy, data from Studies 121 and 131 were analyzed together (See Section 7.1.2.3).

7.1.1.4.3 Analysis Methods

Results presented in the original BLA was based on the pre-specified IA2 (data cutoff date of 10 February 2023) with familywise type 1 error control for the primary and key secondary endpoints. All primary and key secondary endpoints crossed the pre-specified efficacy boundary and therefore demonstrated statistical significance. At the request of FDA, Sponsor performed additional analyses on several efficacy endpoints, including the primary and key secondary endpoints, at the time of the 90-day Safety Update. Results from this most recent data cutoff date of 14 June 2023 are presented in Section 7.2 and are consistent with the findings from IA2, providing further support of the efficacy and safety of exa-cel.

The study included up to three pre-specified IAs to allow early examination of efficacy. The familywise type-I error rate was controlled by an alpha spending approach for tests at interim and final analyses and a sequential testing of the primary and key secondary efficacy endpoints at each IA. The key secondary efficacy endpoint HF12 based on the PES was tested only if the primary efficacy endpoint of VF12 had crossed the efficacy boundary. The key secondary efficacy endpoint VF9 based on the EES was tested one-time and only if both the primary and the key secondary efficacy endpoints of HF12 had crossed the efficacy boundary. VF9 based on the EES was tested with a targeted one-sided alpha of 0.025.

The operating characteristics of the efficacy boundaries and the corresponding alpha spent at each IA and the final analysis to control the type-1 error at one-sided 0.025 across multiple looks, based on the exact binomial distribution for the primary efficacy endpoint (VF12) and the key secondary efficacy endpoint (HF12), both based on the PES, are presented in Table 8.

Table 8: Operating Characteristics of Efficacy Boundaries for the Primary and Key Secondary Efficacy Endpoints in Study 121

Analysis Stage	Efficacy Boundary	Response Rate Boundary (95% CI)	Probability of Crossing Efficacy Boundaries Under Different Response Rates (p_1)[a]			Alpha Spent at Each IA or Final*
			p_1 = 80%	p_1 = 85%	p_1 = 90%	
IA1 (N=10)	9/10	90.0% (55.5%, 99.7%)	37.6%	54.4%	73.6%	1.074%
IA2[b] (N=17)	14/17	82.4% (56.6%, 96.2%)	54.9%	75.6%	91.7%	0.366%
IA3 (N=30)	22/30	73.3% (54.1%, 87.7%)	87.1%	97.2%	99.8%	0.540%
Final (N=45)	31/45	68.9% (53.4%, 81.8%)	97.5%	99.8%	> 99.9%	0.440%
Overall Power			97.9%	99.9%	> 99.9%	
Overall α Spending						2.420%

Analysis Stage	Efficacy Boundary	Response Rate Boundary (95% CI)	Probability of Crossing Efficacy Boundaries Under Different Response Rates (p_1)[a]			Alpha Spent at Each IA or Final*
			p_1 = 80%	p_1 = 85%	p_1 = 90%	

HF12= free from inpatient hospitalization for severe VOCs sustained for at least 12 months after exa-cel infusion; IA=interim analysis; N=total sample size; VF12= not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion.
* Assuming 50% response rate.
a. Marginal probability of crossing the efficacy boundary at a specific IA or final analysis.
b. IA1 was not conducted. Therefore, the alpha planned for this IA was recovered for the subsequent analysis, and the primary (VF12) and first key secondary endpoint (HF12) were considered as statistically significant if the corresponding 1-sided p-value was < 0.0144 during IA2.

Analysis of the primary efficacy endpoint was based on the PES. The proportion of patients achieving VF12 was provided, with 1-sided p-value (against a null hypothesis of 50% response rate) using binomial distribution and 2-sided 95% exact Clopper-Pearson CI.

Analysis of the first key secondary efficacy endpoint (HF12) was based on the PES, and the second key secondary endpoint of VF9 was analyzed based on the EES. Both analyses used the same method as the primary efficacy endpoint.

In addition, to demonstrate that the second key secondary endpoint of VF9 is likely to predict the primary endpoint of VF12, the number and proportion of patients who achieve VF9 in the PES who also achieved VF12 in the PES was provided with the 2-sided 95% exact Clopper-Pearson CI.

The secondary efficacy endpoints analyses were based on the PES and FAS. All analyses for the secondary efficacy endpoints were descriptive. Continuous endpoints were summarized with mean, SD, median, and min/max. Categorical endpoints were summarized with counts and percentages.

A summary of efficacy endpoints and analysis sets used is presented in Table 7 and includes analyses used in both Study 121 and Study 131 (Section 7.1.2).

7.1.2 Study 131 Design

7.1.2.1 Key Enrollment Criteria

Study 131 is a safety and efficacy long term follow-up study to provide up to 15 years of follow-up data after exa-cel infusion. Study 131 enrolled patients who completed or discontinued the pivotal Studies 121 (SCD) and 111 (TDT) following exa-cel infusion.

7.1.2.2 Endpoint Definitions

Study 131 continues the evaluation of safety and efficacy after exa-cel in SCD patients. The primary objective of the study is the long-term safety of exa-cel. The primary endpoints of Study 131 are safety related (new malignancies, new or worsening hematologic disorders,

mortality, and adverse events). Secondary endpoints of Study 131 include efficacy measures that provide longer follow-up of endpoints assessed in Study 121.

In Study 131, efficacy is assessed in secondary and exploratory endpoints which include most of the efficacy endpoints described for the pivotal Study 121 (Section 7.1.1.3)). These secondary endpoints included: severe VOCs; inpatient hospitalizations for severe VOCs; hemolysis markers (reticulocytes/erythrocytes, LDH, haptoglobin, and total and indirect bilirubin); Hb (absolute value) and HbF (in absolute value and %) concentrations; proportion of alleles with intended genetic modifications in peripheral blood; disease-related RBC transfusions; and PROs. Additional exploratory endpoints assessed in Study 131 included Hb fractionation (supportive of Hb and HbF assessments), circulating erythrocytes expressing γ-globin (HbF; F-cells), and blood erythropoietin level.

7.1.2.3 Analysis Methods

Efficacy endpoints in Study 131 were descriptive. Efficacy endpoints using pooled data from Study 121 and Study 131 were analyzed based on the respective datasets [SCD]PES and/or [SCD]FAS at the time of parent study data cut-off dates. The continuous endpoints were summarized with mean, SD, median, min, and max; and categorical endpoints were summarized with counts and percentages.

7.2 Study 121/131 Results

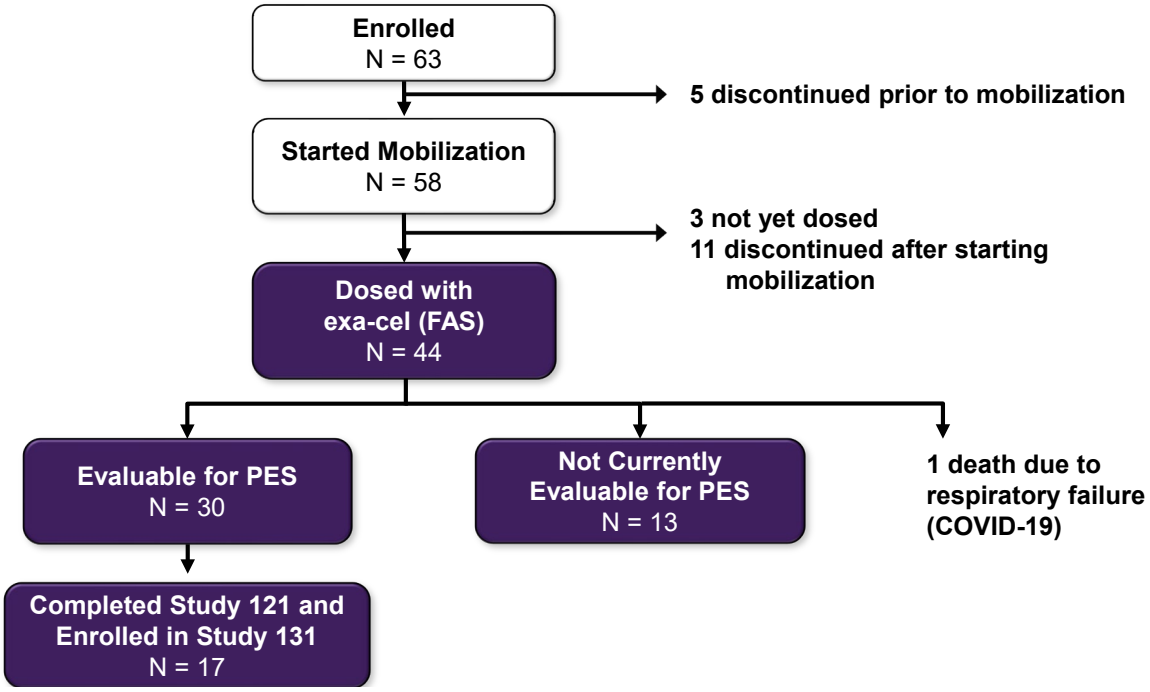
As discussed in Section 7.1.1.4.3, results from Study 121 based on prespecified IA2 were statistically significant for the primary and both key secondary endpoints. Results reported below are results based on an updated data-cutoff date after the pre-specific IA2 performed at the request of the FDA, which includes 30 patients with 18 months of follow-up in the PES (1 patient had 17.8 months of follow-up). These updated results are consistent with findings at IA2 demonstrating transformational and durable clinical benefit after infusion with exa-cel. Study 131 includes efficacy measures that provide long-term follow-up of secondary endpoints assessed in Study 121.

7.2.1 Patient Disposition

At the updated 14 June 2023 data cutoff date, Study 121 had completed enrollment with 63 patients enrolled (Figure 8). Of these, 58 patients had started mobilization. Forty-four of these patients had received exa-cel and are included in the [SCD]FAS, and 30 patients had sufficient follow-up after exa-cel infusion to be included in the [SCD]PES. Eleven participants discontinued after the start of mobilization but before start of myeloablative conditioning and did not receive exa-cel; none of the discontinuations were due to AEs. Of these 11 participants, 6 discontinued as they were unable to achieve a full dose of the drug product; 1 participant discontinued due to no longer meeting eligibility criteria for renal function; 1 participant discontinued due to non-compliance, and 3 participants withdrew consent.

Of the 44 patients who received exa-cel, seventeen patients completed Study 121, all of whom enrolled in Study 131. After the 14 June 2023 data cutoff date, dosing of all planned patients (46 in total) was completed in Study 121.

Figure 8: Patient Disposition for Studies 121 and 131 (Enrolled Set and [SCD]Enrolled Set)



EES=Early Efficacy Set; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; PES=Primary Efficacy Set; SCD=sickle cell disease; VF9= not experienced any (i.e., absence of) severe VOC for at least 9 consecutive months after exa-cel infusion.
Note: Of the 3 patients not yet dosed in Study 121 as of the data cutoff date, 2 subsequently were dosed with exa-cel and 1 discontinued prior to dosing.
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Note: In addition to the PES, the EES (N=32; not shown in figure) is a subset of the FAS (N=44) were evaluable for the intermediate clinical endpoint (VF9; Section 7.2.10.2).
a. The FAS included all patients who received exa-cel infusion.
b. Reason for discontinuation after exa-cel: death due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.

7.2.2 Patient Demographics and Baseline Medical Characteristics

Overall, the patient demographics and baseline medical characteristics of participants in Studies 121 and 131 are representative of the US patient population with SCD who would be treated with exa-cel (Table 9).

Patient demographics was similar between the PES and FAS. For the FAS, the median (range) age was 20 (12 to 34) years. There were 12 (27.3%) adolescent patients (ages 12 to <18 years). Most patients were Black or African American (86.4%), and patients were balanced by sex.

Table 9: Patient Demographics (Study 121, PES and FAS)

Demographics	PES N=30	FAS N=44
Sex, n (%)		
Male	16 (53.3)	24 (54.5)
Female	14 (46.7)	20 (45.5)
Age at screening (years)		
Mean (SD)	22.1 (6.0)	21.2 (6.1)
Median (min, max)	21.0 (12, 34)	20.0 (12, 34)
Age category at screening, n (%)		
12–<18 years (adolescent)	6 (20.0)	12 (27.3)
18–35 years (adult)	24 (80.0)	32 (72.7)
Race, n (%)		
White	1 (3.3)	3 (6.8)
Black or African American	26 (86.7)	38 (86.4)
Other	3 (10.0)	3 (6.8)
Ethnicity, n (%)		
Hispanic or Latino	2 (6.7)	2 (4.5)
Not Hispanic or Latino	27 (90.0)	41 (93.2)
Not collected per local regulations	1 (3.3)	1 (2.3)

FAS=Full Analysis Set; N=total sample size; PES=Primary Efficacy Set.

Baseline medical characteristics were representative of the overall US patient population with SCD who would be treated with exa-cel (Table 10).

Table 10: Baseline Characteristics (Study 121, PES and FAS)

Baseline Characteristics	PES N=30	FAS N=44
Genotype, n	30	44
β^S/β^S, n (%)	29 (96.7)	40 (90.9)
β^S/β^0, n (%)	1 (3.3)	3 (6.8)
β^S/β^+, n (%)	0	1 (2.3)
HbF (g/dL), n	29	43
Mean (SD)	0.5 (0.4)	0.5 (0.4)
Median (min, max)	0.4 (0.0, 1.5)	0.4 (0.0, 1.5)
HbF (%), n	30	44
Mean (SD)	5.2 (3.8)	5.4 (3.9)
Median (min, max)	5.3 (0.0, 14.7)	5.0 (0.0, 14.7)
Total Hb (g/dL), n	29	43
Mean (SD)	9.0 (1.6)	9.1 (1.6)

Baseline Characteristics	PES N=30	FAS N=44
Median (min, max)	9.4 (5.7, 12.6)	9.4 (5.7, 12.6)
Annualized rate[a] of severe VOCs, n	30	44
Mean (SD)	3.9 (2.1)	4.1 (3.0)
Median (min, max)	3.3 (2.0, 9.5)	3.5 (2.0, 18.5)
Annualized rate[a] of inpatient hospitalizations for severe VOCs, n	30	44
Mean (SD)	2.7 (2.0)	2.7 (2.0)
Median (min, max)	2.0 (0.5, 8.5)	2.5 (0.5, 9.5)
Annualized duration[b] of inpatient hospitalizations for severe VOCs (days), n	30	44
Mean (SD)	17.1 (14.3)	19.7 (21.9)
Median (min, max)	12.3 (2.0, 64.6)	14.0 (2.0, 136.5)
Annualized units[c] of RBCs transfused for SCD-related indication, n	30	44
Mean (SD)	8.4 (14.9)	11.3 (18.4)
Median (min, max)	3.3 (0.0, 75.5)	5.0 (0.0, 86.1)
Weight (kg), n	30	44
Mean (SD)	65.5 (14.9)	65.7 (17.3)
Median (min, max)	65.5 (43.0, 95.0)	67.0 (34.0, 116.0)
Haptoglobin (g/L), n	29	43
Mean (SD)	0.1 (0.1)	0.1, (0.2)
Median (min, max)	0.0 (0.0, 0.3)	0.0 (0.0, 0.9)
Lactate dehydrogenase (U/L), n	29	43
Mean (SD)	474.3 (200.3)	479.3 (224.4)
Median (min, max)	448.0 (168.0, 913.0)	419.0 (168.0, 1228.0)

EAC=endpoint adjudication committee; FAS=Full Analysis Set; Hb=hemoglobin; HbF=fetal hemoglobin; n=size of subsample; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VOCs=vaso-occlusive crises.
Notes: Baseline severe VOCs, inpatient hospitalizations for severe VOCs, and RBC transfusions were based on the 2 years before the most recent screening. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included. Hemoglobin measurements were from central laboratories. For hemolysis markers, values with “below detectable limit” were entered as 0.
a. Annualized rate=total number of events/number of years.
b. Annualized duration=total duration of events/number of years.
c. Annualized units=total units/number of years.

7.2.3 Primary Endpoint — Proportion of Patients without Severe VOC for ≥ 12 Consecutive Months after Treatment (VF12)

Study 121 met its primary endpoint of VF12 with statistical significance at IA2, and results as of the 14 June 2023 data cut-off date remained consistent with the prespecified findings. Specifically, 29 of 30 (96.7%) patients in the PES achieved VF12 (95% CI: 82.8%, 99.9%;

1-sided p < 0.0001 against a 50% response rate) (Table 11). Sixteen of the 17 (94.1%) patients who continued into Study 131 remained VOC-free throughout the duration of follow-up.

In adolescent patients (ages 12 to <18 years), 6 of 6 (100%) achieved VF12 (See Section 7.2.11 for details).

The one patient in the PES who did not achieve VF12 still received meaningful clinical benefit from exa-cel therapy. This patient had a complex medical history including SCD-related chronic pain. Prior to exa-cel, the patient had a history of 3.5 hospitalizations per year during the 2 years before Study 121 with an average of 28.5 days per year in the hospital. After exa-cel, this patient had no hospitalizations for VOC (see Section 7.2.4.1 [HF12]; additional details on this patient are presented in Section 7.2.5.3.1).

Table 11: Primary Endpoint Results: Proportion of Patients Who Achieved VF12 (Study 121, PES)

Primary Endpoint, n (%)	PES N=30
Patients who achieved VF12	29 (96.7)
2-sided 95% CI	(82.8, 99.9)
1-sided p-value	< 0.0001[a]

EAC=endpoint adjudication committee; exa-cel=exagamglogene autotemcel; N=total sample size; n=size of subsample; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VF12=absence of any severe VOCs for at least 12 consecutive months; VOC=vaso-occlusive crisis.
Notes: The evaluation of VF12 started 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The prohibited medication treatment period was excluded from the VOC-free duration. The percentage of patients who achieved VF12 was calculated relative to the number of patients in the PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.
a. This was against a 50% response rate.

7.2.4 Key Secondary Endpoints

Study 121 met both key secondary endpoints of HF12 and VF9 with statistical significance at IA2, and results as of the data cutoff date of 14 June 2023 remained consistent with the prespecified findings. The key secondary endpoints were tested hierarchically.

7.2.4.1 First Key Secondary Endpoint — Elimination of Hospitalizations Due to VOCs for ≥ 12 Consecutive Months after Treatment (HF12)

Assessment of inpatient hospitalization for VOCs is a clinically meaningful endpoint, as VOC events are the most common cause of hospitalizations for individuals with SCD.[46, 48, 49, 86] The primary efficacy endpoint definition of VOCs is broad and includes events treated in an outpatient clinic, emergency room, or inpatient hospital setting. The evaluation of the subset of VOCs that require inpatient hospitalization is a stringent efficacy measure and allows assessment of the most severe events associated with the greatest mortality risk and informs the overall impact of exa-cel treatment.[86, 87]

Study 121 met the key secondary efficacy endpoint of free from inpatient hospitalization for severe VOCs for ≥ 12 consecutive months following exa-cel infusion (HF12). All (100%) 30 patients in the PES achieved HF12 (95% CI: 88.4%, 100%; 1-sided p < 0.0001 against a 50% response rate; Table 12).

In the 2 years before screening (i.e., starting Study 121), patients in the PES averaged (range) 2.7 (0.5 to 8.5) separate inpatient hospitalizations per year for severe VOCs. Moreover, patients spent an average of 17.1 (range: 2.0 to 64.6) days per year as inpatients in a hospital during the same 2 years before Study 121 (Table 10). Therefore, all patients being free from inpatient hospitalization for at least 12 months is highly clinically meaningful.

Table 12: Key Secondary Endpoint Results: Proportion of Patients Who Achieved HF12 (Study 121, PES)

Patients Achieving HF12, n (%)	PES N=30
Proportion of Patients who achieved HF12	30 (100)
2-sided 95% CI	(88.4, 100.0)
1-sided p-value	< 0.0001[a]

Exa-cel=exagamglogene autotemcel; HF12=free from inpatient hospitalization for severe VOCs for at least 12 months after exa-cel infusion; IA=interim analysis; N=total sample size; n=size of subsample; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease.
Notes: The evaluation of HF12 started 60 days after last RBC transfusion for post-transplant support or SCD management. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.
a. Statistical significance was established at IA2; this was against a 50% response rate

7.2.4.2 Second Key Secondary Endpoint — Proportion of Patients without Severe VOC for ≥ 9 Consecutive Months after Treatment (VF9)

Study 121 met the second key secondary efficacy endpoint of VF9 with 31 of 32 patients (96.7%) in the EES free from severe VOCs for ≥ 9 consecutive months after infusion with exa-cel (95% CI: 83.8%, 99.9%; 1-sided p < 0.0001 against a 50% response rate; Table 13).

VF9 was tested in the EES as an intermediate clinical endpoint that is reasonably likely to predict VF12 (see Section 7.2.3). All patients in the PES who achieved VF9 also achieved VF12.

Table 13: Key Secondary Endpoint Results: Proportion of Patients Who Achieved VF9 (Study 121, EES)

Patients Achieving VF9, n (%)	EES N=32
Patients who achieved VF9 in the EES Population	31 (96.9)
2-sided 95% CI	(83.8, 99.9)
1-sided p-value	< 0.0001[a]

EAC=endpoint adjudication committee; EES=Early Efficacy Set; IA=interim analysis; N=total sample size; n=size of subsample; RBC=red blood cell; SCD=sickle cell disease; VF9=absence of any severe VOCs for ≥ 9 consecutive months after exa-cel infusion; VOC=vaso-occlusive crisis.
Notes: The evaluation of VF9 started 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The prohibited medication treatment period was excluded from the VOC-free duration. The percentage of patients who achieved VF9 was calculated relative to the number of patients in the EES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.
a. Statistical significance was established at IA2; this was against a 50% response rate.

7.2.5 Duration VOC-Free and Hospitalization- Free

To evaluate the durability of clinical efficacy, the duration VOC-free and the duration hospitalization-free were evaluated as secondary endpoints. To fully describe the long-term durability of exa-cel, the data below include the total follow-up duration after exa-cel infusion in Study 121 and Study 131. This population is referred to as the SCD[PES].

7.2.5.1 Duration of VOC-Free among Patients who Achieved VF12

For the 29 patients who achieved VF12, the mean (SD) VOC-free duration was 22.4 (7.2) months, including follow-up in Study 131 (Table 14; Figure 9). Twenty-eight of 29 (96.6%) patients who achieved VF12 remained VOC-free throughout follow-up in Studies 121 and 131, up to 45.5 months starting 60 days after the last RBC transfusion, demonstrating the durability of treatment effect.

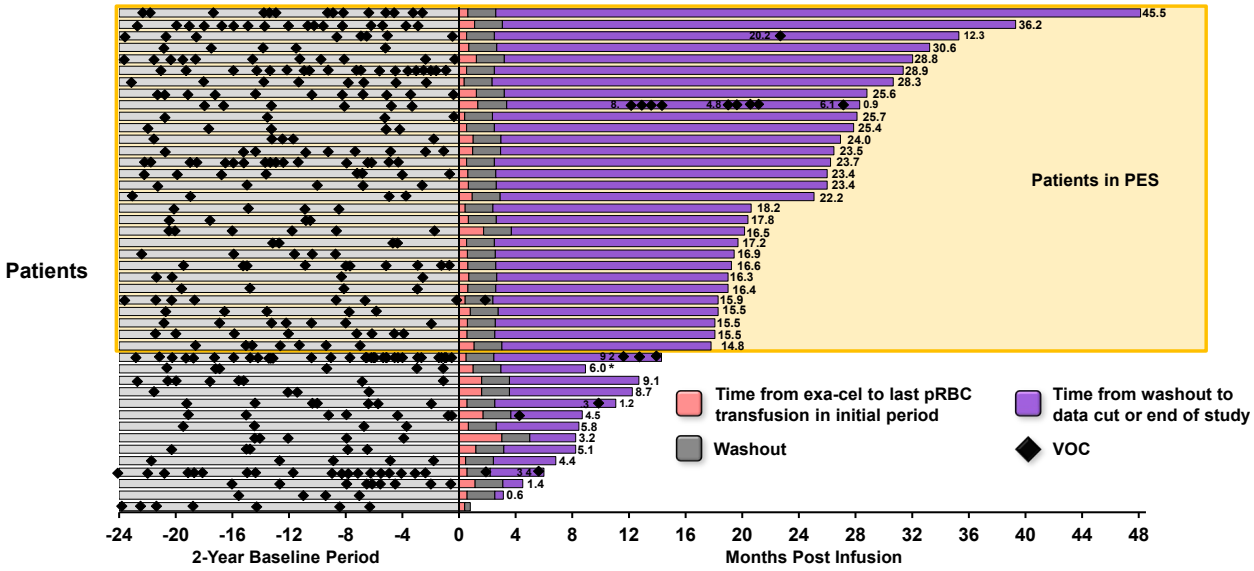
One patient achieved VF12 and remained VOC-free for 23 months after exa-cel infusion, then had a single event adjudicated as a VOC by the EAC in the setting of parvovirus infection. This patient has subsequently been VOC free for 12.3 months, up to the data cutoff date (additional details of this patient are presented in Section 7.2.5.3.1).

Table 14: Duration of Severe VOC-Free for Patients Who Achieved VF12 (Studies 121 and 131, [SCD]PES)

Category	[SCD]PES N=30
Patients who achieved VF12, n (%)	29 (96.7)
Duration of severe VOC-free (months)	
Mean (SD)	22.4 (7.2)
Median (min, max)	22.2 (14.8, 45.5)

EAC=Endpoint Adjudication Committee; exa-cel=exagamglogene autotemcel; N=total sample size; n=size of subsample; RBC=red blood cell; PES=Primary Efficacy Set; SCD=sickle cell disease; SD: standard deviation; VF12: absence of any severe VOCs for at least 12 consecutive months; VOC: vaso-occlusive crisis.
Notes: If there were multiple severe VOC free periods, the longest severe VOC free period was used in the summary. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included.

Figure 9: Duration of Severe VOC-Free in Individual Patients Who Received Exa-cel (Studies 121 and 131, [SCD]FAS)



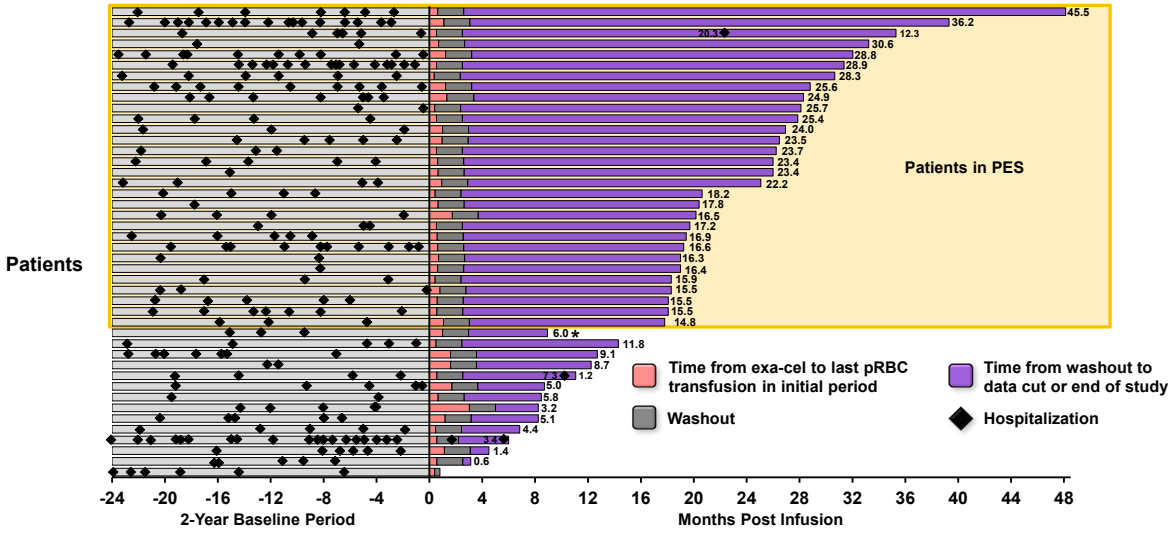
EAC=Endpoint Adjudication Committee; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VOC=vaso-occlusive crisis.
* One patient died from respiratory failure due to COVID-19 infection 6.0 months after the end of the RBC 60-day RBC transfusion washout period; the adverse event was considered unrelated to exa-cel.
Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria were included. Severe VOC-free duration starts 60 days after the last RBC transfusion for post-transplant support or SCD management. The numbers to the right of the purple bars indicate the duration of VOC free starting 60-day after last RBC transfusion or from the last VOC. The RBC washout period refers to the 60 days immediately following the last RBC transfusion for post-transplant support or SCD management.

7.2.5.2 Duration of Hospital-Free Due to VOC among Patients Treated with Exa-cel

For the 30 patients who achieved HF12, the mean (SD) hospitalization free duration was 22.5 (7.0) months, including follow-up in Study 131. Twenty-nine of 30 patients who achieved HF12 remained free of hospitalizations due to VOCs throughout follow-up in Studies 121 and 131, up to 45.5 months starting 60 days after the last RBC transfusion, again demonstrating the durability of treatment effect (Figure 10).

The one patient who achieved HF12 and then had an hospitalization is the same patient described above who had a single event in the setting of a parvovirus infection approximately 23 months after exa-cel infusion, and has subsequently had no additional hospitalizations due to VOC for 12.3 months up to the data cutoff date (additional details of this patient are presented in Section 7.2.5.3.1).

Figure 10: Duration of Hospital-Free for VOCs in Individual Patients Who Received Exa-cel (Studies 121 and 131 [SCD]FAS)



EAC=Endpoint Adjudication Committee; exa-cel= exagamglogene autotemcel; FAS=Full Analysis Set; PES=Primary Efficacy Set; pRBC: packed red blood cell; RBC: red blood cell; SCD: sickle cell disease; VOC: vaso-occlusive crisis.
* One patient died from respiratory failure due to COVID-19 infection 6.0 months after the end of the RBC 60-day RBC transfusion washout period; the adverse event was considered unrelated to exa-cel.
Notes: Only severe VOCs that were adjudicated by the EAC as meeting the protocol criteria were included. Hospitalization-free duration starts 60 days after the last RBC transfusion for post-transplant support or SCD management. The numbers to the right of the purple bars indicate the duration of hospitalization free starting 60-day after last RBC transfusion or from the last hospitalization for VOC. The RBC washout period refers to the duration between the last RBC transfusion for post-transplant support or SCD management to the start of the hospitalization free period.

7.2.5.3 Discussion of Patients with VOC Events after Exa-cel Infusion

Pain events presenting as VOCs are known to occur in a subset of SCD patients after allo-HSCT, including patients after successful allo-HSCT who have achieved high donor chimerism and low-to-no detectable HbS and have therefore achieved a cure for their disease.[86, 88-91] This

includes both early events in the peri-transplant period (i.e., when patients are still recovering from the transplant procedure including myeloablation and/or prior to full reconstitution of RBCs) as well as later events that may occur 1 to 2 years after allo-HSCT.

Additionally, interpretation of pain events after HSCT for SCD is complicated because post-transplant pain can be caused by factors other than VOC events. Examples include exacerbations of pre-existing conditions, such as acute exacerbation of chronic pain (e.g., from avascular necrosis), and pain hypersensitivity/hyperalgesia syndromes that all represent features of pre-existing SCD related end-organ damage. Given these features, attribution of pain to a VOC event directly related to HbS associated vaso-occlusion can, in some cases, be difficult in the post- HSCT setting. To minimize bias, in Study 121, an independent EAC adjudicated each individual VOC based on the protocol definition.

While the EAC adjudicated each VOC individually, the overall clinical situation of the patients can provide context to additional factors that inform a more comprehensive view of the overall efficacy response after exa-cel treatment. Individual patient descriptions are described below for the patients with events adjudicated as VOCs that occurred after the 60-day RBC washout period following exa-cel infusion:

7.2.5.3.1 Discussion of Events Adjudicated As VOCs in Patients in the Primary Efficacy Set

After exa-cel infusion, only 2 of the 30 patients in the [SCD]PES had events adjudicated as VOCs after the 60-day RBC washout period. However, both patients experienced clinical benefit from exa-cel therapy, as evidenced by achieving VF12 and/or HF12 with dramatically reduced numbers of events and supported by stable HbF (%) levels and allelic editing that are consistent with the overall patient population in the PES:

- The first patient, previously described in Section 7.2.5.1, had a single VOC event approximately 23 months after exa-cel in the context of a parvoviral infection and achieved both VF12 and HF12. Prior to exa-cel, this patient averaged 4 VOCs and 3 hospitalizations for VOCs per year during the 2 years before starting Study 121, with an average of 17.5 days per year in the hospital. The single event in this patient at approximately 23 months after exa-cel was associated with a documented Parvovirus B19 infection. Parvovirus B19 is well known for causing severe, life-threatening infections in SCD patients often resulting in profound anemia due to parvovirus associated RBC aplasia typically requiring prolonged RBC transfusion support, prolonged hospitalization often in an intensive care unit, and increased risk of ACS and life threatening complications.[40, 92, 93] In contrast, this patient recovered uneventfully without any complications and without the need for RBC transfusion, which was a milder clinical course of parvovirus B19 infection than would otherwise be expected in SCD.[40] The patient's total Hb decreased from 14.1 to 9.7 g/dL during the event, consistent with Parvovirus B19 associated anemia, and then had a spontaneous recovery of Hb levels to 12 g/dL within 40 days after the event. This rapid, spontaneous recovery of Hb in the absence of RBC transfusion highlights the normal function and capacity of the exa-cel graft to respond appropriately to a hematopoietic challenge. In addition, the overall clinical course of this event highlights the protection from severe complications provided by exa-cel. Overall, the patient has had a robust increase in HbF after exa-cel therapy that was consistent with other patients in the PES. Specifically, HbF (%) levels surpassed 30% starting at Month 3 and were sustained throughout the

duration of follow-up. At the most recent Month 33 study visit, HbF (%) was stable at 35.7% and total Hb was stable at 13.5 g/dL, consistent with other subjects in the study who have achieved VF12 and HF12. Additionally, the patient had stable blood and bone marrow allelic editing over time (71.4% at Month 6 and 73.5% at Month 24 in peripheral blood; 80.4% at Month 6 and 81.0% at Month 24 in bone marrow) consistent with other patients in the PES. As of the data cutoff date, the patient has remained VOC free for 12.3 months after the 1 event.

- The second patient, previously described in Section 7.2.3, did not achieve VF12, and experienced 9 events adjudicated as VOCs after exa-cel. This patient still received clinical benefit from exa-cel and achieved HF12 with no hospitalizations due to VOCs in the 28.3 months of follow-up after exa-cel therapy. The patient had a complex medical history, including SCD-related chronic pain. In the 2 years prior to Study 121, the patient had a history of 3 VOCs per year and 3.5 hospitalizations per year, with an average of 28.5 days per year in the hospital. The patient achieved clinical benefit as evidenced by achieving HF12 in the context of a dramatic overall reduction in hospitalizations after exa-cel. Moreover, approximately 20 months after exa-cel infusion, the patient underwent an uncomplicated Heller cardiomyotomy (a surgical procedure to treat pre-existing achalasia) under general anesthesia without any preoperative optimization (e.g., RBC transfusion), which would have been otherwise required for patients with SCD. The patient experienced none of the postoperative complications that are common for patients with SCD — e.g., ACS, infections, and VOCs.[94] This patient also had robust increases in HbF after exa-cel treatment and allelic editing that were consistent with other patients in the PES. Specifically, HbF (%) levels surpassed 40% starting at Month 3 and were sustained throughout the duration of follow-up. At the most recent Month 24 study visit (Study Day 729), HbF (%) was stable at 49.1% and total Hb was stable at 11.9 g/dL, consistent with other subjects in the study who have achieved VF12 and HF12. The patient had stable peripheral blood and bone marrow allelic editing over time (75.9% at Month 6 and 80.7% at Month 24 in peripheral blood; 91.7% at Month 6 and 92.9% at Month 24 in bone marrow) consistent with other patients in the PES.

7.2.5.3.2 Discussion of Events Adjudicated as VOC events in Patients not in the PES

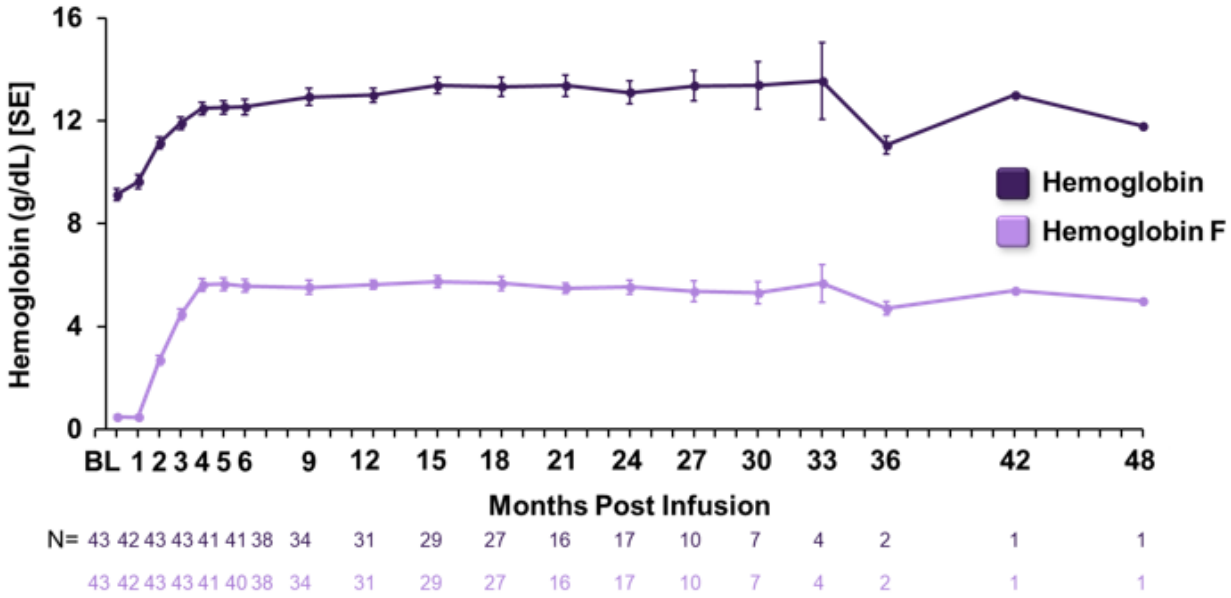
There are 14 additional patients who received exa-cel that are not yet in the PES because they do not yet have sufficient follow-up time after exa-cel to evaluate the primary efficacy endpoint VF12 (16 months of follow-up after exa-cel). Of the 14 patients, 4 patients have experienced VOCs early after the 60-day RBC washout period following exa-cel infusion (Figure 9). These patients have HbF % and allelic editing levels similar to patients in the PES (see Figure 12, Figure 14, and Figure 15) and retain the potential to achieve VF12 and/or HF12.

7.2.6 Hematologic Parameters

7.2.6.1 HbF (%) and Total Hb Levels over Time

After exa-cel infusion, patients achieved rapid, robust, and durable levels of HbF (%) that are associated with clinical benefit, including absence of VOCs (Figure 11).

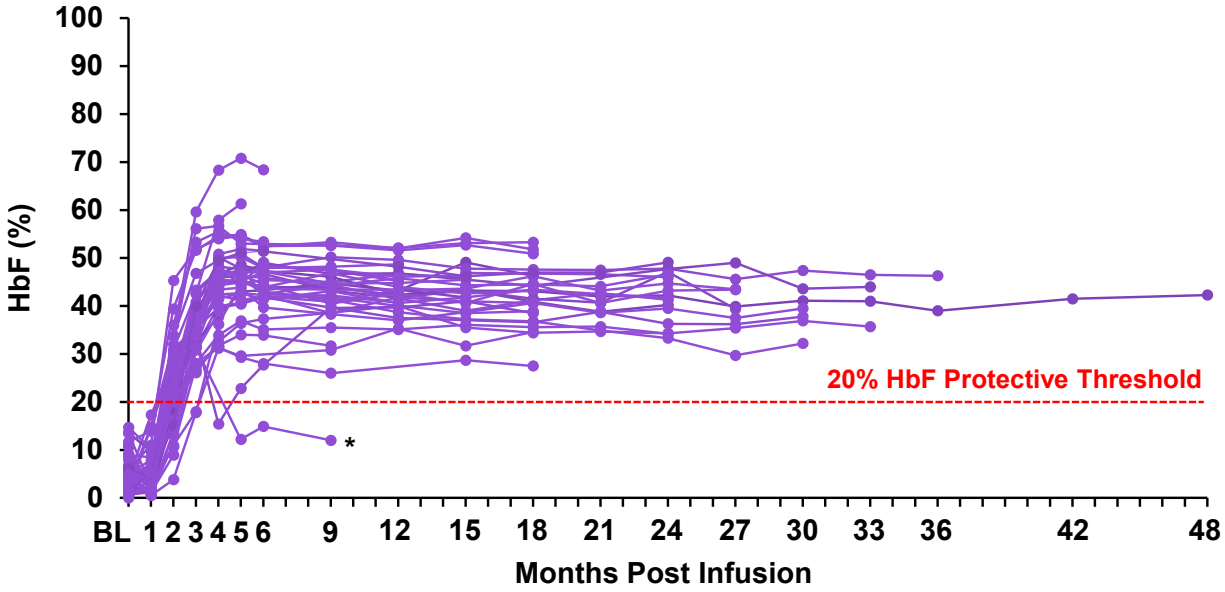
Figure 11: Summary of Total Hb and HbF over Time (Studies 121 and 131, [SCD]FAS)



BL=baseline; FAS=Full Analysis Set; Hb=hemoglobin; HbF=fetal hemoglobin; SE=standard error.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization in Study 121. Analysis visit was used in the figure.

The MOA of exa-cel treatment is to reactivate HbF production (Section 3.5). Importantly, HbF (%) levels ≥ 20% are protective against disease complications, including VOCs, as documented in cases in which people with SCD genotypes also co-inherit HPFH (Section 3.3). Therefore HbF (%) over time was assessed as a biomarker of successful treatment and a surrogate for efficacy that is reasonably likely to predict clinical benefit (Section 7.2.10.1). Mean HbF (%) was maintained generally at ≥ 40% from Month 6 throughout the duration of follow-up (Figure 12).

Figure 12: HbF (%) over Time in Individual Patients (Studies 121 and 131 [SCD]FAS)



BL=baseline; FAS=Full Analysis Set; HbF=fetal hemoglobin; SE=standard error.
Notes: Dashed red line=20% HbF threshold for protection against disease (See Section 3.3). Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization in Study 121. Analysis visit was used in the figure.
* Indicates Subject [redacted] who died due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.

Overall, increases in HbF and total Hb occurred early and were maintained over time at clinically significant levels:

- The mean (SD) total Hb levels were 11.9 (1.5) g/dL at Month 3 and were maintained with mean ≥ 11.1 g/dL from Month 6 onward.
- The mean (SD) proportion of total Hb composed of HbF (HbF [%]) was 36.9% (9.0%) at Month 3 and was generally maintained at ≥ 40% from Month 6 through the duration of follow-up.

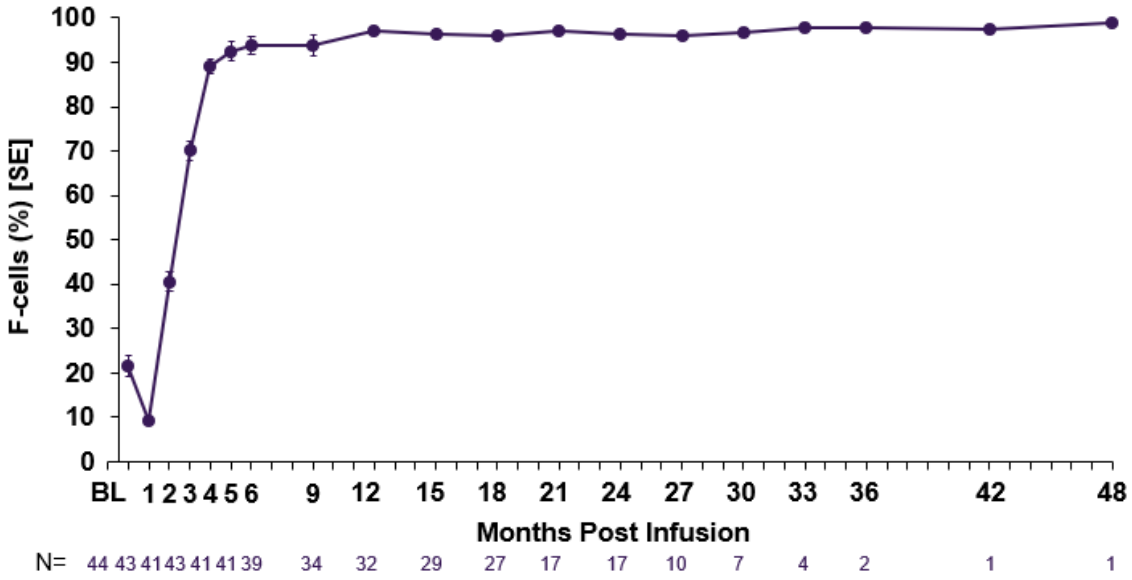
These observations of rapid and robust increases in mean levels of total Hb and HbF (%) that were maintained over time were similar across patients, regardless of their duration of follow-up. Therefore, patients with shorter follow-up who were not yet evaluable for assessment of the primary endpoint at the time of data cutoff date are expected to maintain clinically meaningful total Hb and HbF (%) levels and have similar clinical benefit as the patients in the [SCD]PES.

7.2.6.2 Change in Proportion of F-Cells over Time

Measurement of the proportion of F-cells allows measurement of the distribution of HbF across the RBCs in circulation. The high percentage of F-cells (≥ 90%) observed after exa-cel infusion is consistent with a pancellular distribution of HbF, indicating that almost all RBCs in circulation are derived from exa-cel, and recapitulates what is known in SCD HPFH to be associated with absence of VOCs (Section 3.3).[27, 28, 32]

The ratio of F-cells grew consistently in relation to increases in HbF. The mean (SD) proportion of F-cells was maintained with mean ≥ 93% from Month 6 and ≥ 96% from Month 12 through the 4-year follow-up (Figure 13).

Figure 13: Mean F-Cell Level (%) over Time (Studies 121 and 131, [SCD]FAS)



FAS=Full Analysis Set; F-cells=circulating RBCs expressing detectable levels of HbF; RBC=red blood cell; SCD=sickle cell disease; SE=standard error.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization in Study 121. Analysis visit was used in the figure.

This rapid increase in F-cell % also occurred among patients in the two [SCD]FAS subsets: (1) the [SCD]PES (i.e., patients who have been followed for ≥ 16 months after exa-cel infusion; N=30), and (2) those who were not yet eligible for the [SCD]PES (i.e., patients with < 16 months follow-up; N=14). Taken together, these data indicate that all patients follow similar kinetics of efficacy and achieve F-cell levels that correlate with clinical benefit. Thus, patients with shorter follow-up who are not yet evaluable for the primary endpoint are expected to maintain these F-cell (%) levels and have consistent, durable clinical benefit.

7.2.6.3 Reduction in RBC Transfusions Starting 12 Months after Treatment

Consistent with HbF increases from exa-cel that ameliorated anemia, patients in the PES no longer required RBC transfusions for any SCD-related indication starting 12 months after treatment. This was a 100% reduction from baseline in RBC transfusions: at baseline, patients in the PES were receiving a yearly mean (SD) of 8.4 (14.9) units of RBC transfusions. Twelve months after exa-cel treatment, the number was zero.

7.2.7 Allelic Editing

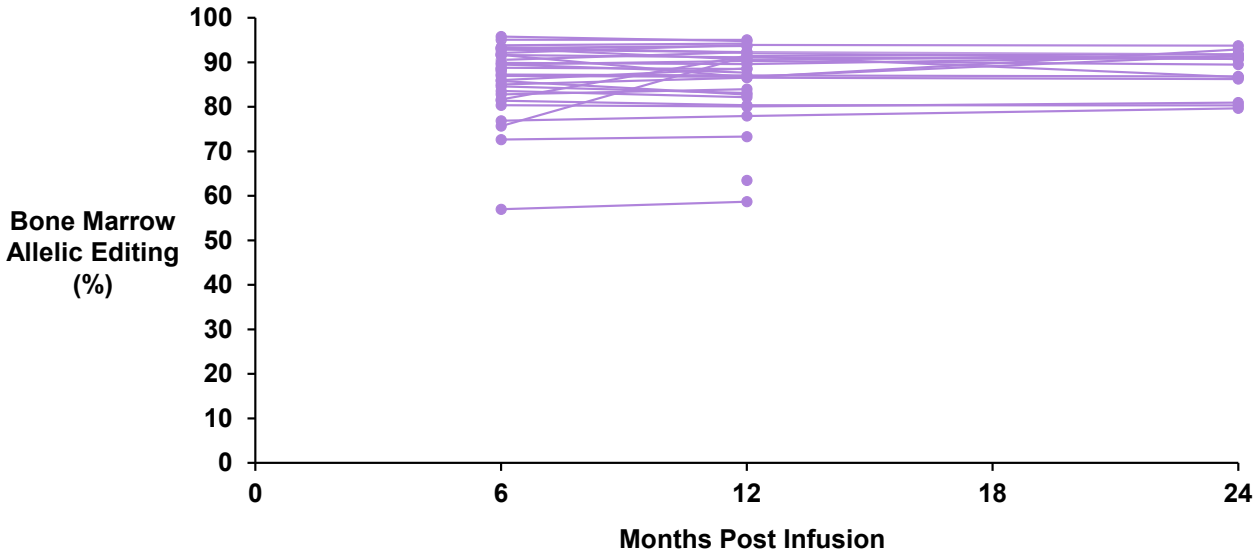
The proportion of alleles with the intended genetic modification (allelic editing) in bone marrow and in peripheral blood over time indicate durable engraftment of edited LT-HSCs and reflect

the permanent nature of the intended edit. Results in bone marrow and peripheral blood remained consistent among patients in the two subsets of the [SCD]FAS: the [SCD]PES (N=30) and those not yet eligible for the [SCD]PES (N=14). Patients who were not yet evaluable for the primary endpoint are also expected to maintain percent allelic editing over time, based on the permanent nature of the intended edit.

7.2.7.1 Bone Marrow Allelic Editing over Time

In the [SCD]FAS, allelic editing in the bone marrow remained stable for the duration of follow-up (up to 2 years), indicating successful engraftment of edited LT-HSCs and supporting durability of effect (Figure 14). Patients who had the lowest levels of bone marrow editing at Months 12 and 24 achieved the primary endpoint of VF12. The stable, durable allelic editing is consistent with stable, durable HbF production over time and indicates that the clinically meaningful effect of elimination of VOCs will be durable.

Figure 14: Individual Bone Marrow Allelic Editing (%) over Time (Study 121, FAS)

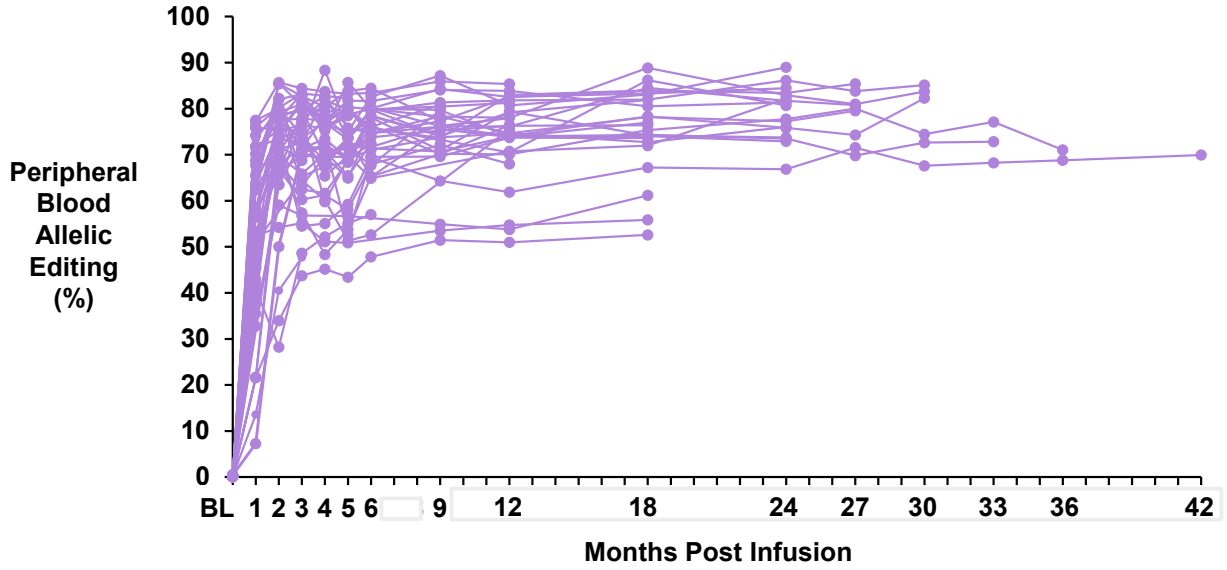


FAS=Full Analysis Set.
Notes: Analysis visit was used in the figure.

7.2.7.2 Peripheral Blood Allelic Editing over Time

Similar to $CD34^+$ bone marrow cells, allelic editing in peripheral blood remained stable for the duration of follow-up (up to 3.5 years, as measured for peripheral blood), indicating stable engraftment of edited LT HSCs and supporting durability of effect (Figure 15). As with bone marrow allelic editing, patients who had the lowest levels of peripheral blood (nucleated cells) editing at Months 12 and 24 achieved the primary endpoint of VF12. The stable, durable allelic editing is consistent with stable, durable HbF production over time and indicates that the clinically meaningful effect of elimination of VOCs will be durable.

Figure 15: Peripheral Blood Allelic Editing (%) in Individual Patients over Time (Studies 121 and 131, [SCD]FAS)



BL=baseline; FAS=Full Analysis Set; SCD=sickle cell disease.
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization in Study 121. Analysis visit was used in the figure.

7.2.8 Markers of Hemolysis

Reduction in hemolysis is an additional benefit of exa-cel infusion. In SCD, RBCs are prone to hemolysis, which is associated with significant morbidity and mortality.[49] The key mechanism of hemolysis in SCD is intravascular hemolysis, which can be measured by LDH and haptoglobin.[38, 39] Assessments of these biomarkers show that exa-cel treatment leads to normalization of hemolysis assessments, which is expected to correlate with reduced organ damage[27, 28, 31] a reduction in other disease complications.

7.2.8.1 Decrease in LDH over Time

Elevated LDH, a hemolytic marker, is associated with increased morbidity and mortality in SCD.[13, 37] At baseline, patients in the [SCD]PES (N=30) had elevated mean (SD) LDH levels of 1.7 (0.7) times the ULN. Following exa-cel infusion, mean LDH levels progressively decreased and normalized by Month 9. Thereafter, Mean LDH levels remained within the normal range through 4 years of follow-up.

7.2.8.2 Increase in Haptoglobin Starting 6 Months after Therapy

Haptoglobin is a sensitive measure of intravascular hemolysis and is generally low-to-undetectable in patients with SCD.[31, 95] Consistent with this, patients in the [SCD]PES (N=30) had low mean (SD) haptoglobin levels of 0.4 (0.4) × lower limit of normal at baseline, and only 22 (73.3%) patients had detectable haptoglobin at baseline. Following exa-cel infusion, 29 of 30 patients (96.7%) with follow-up data generally had detectable haptoglobin levels at Month 6 through follow-up.

Conclusions from Hemolysis Markers

Overall, the data show that treatment with exa-cel leads to normalization of hemolysis assessments. The normalization of hemolysis after exa-cel infusion is consistent with the known protective effect of HbF and is consistent with the observed pancellular distribution of HbF after exa-cel infusion. Resolution of hemolysis is expected to correlate with reduced end- organ damage[27, 28, 31] and a reduction in other disease complications.

7.2.9 Patient-Reported Outcomes

Findings from PROs are based on results as assessed at the second IA2 (data cutoff date of 10 February 2023). Results of PROs were not updated at the 14 June 2023 data cutoff date.

Adult participants completed four PRO instruments to assess the patient perspective on health status and quality of life. Instruments used were EQ-5D-5L, FACT-BMT, Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me), and Pain NRS. As determined by an FDA-convened panel, in partnership with the American Society of Hematology, the three key PRO domains in SCD are: pain (acute and chronic), affect (emotional impact, sleep quality, and fatigue), and functioning (social, physical, and cognitive functioning, as well as self-efficacy for disease management and occupational function).[96] Most of these domains are included in one or more PRO tools used in Study 121 and show clear clinical benefit.

ASCQ-Me is validated in SCD, and the other instruments are well-established tools used frequently across numerous conditions, including SCD and HSCT in hematologic malignancies.[97, 98] The minimal clinically significant difference (MCID) thresholds are SCD-specific for ASCQ-Me but not for the other tools; however, they are largely consistent across numerous hematologic conditions.[98]

The following sections discuss PRO data through 2 years of follow-up.

EQ-5D-5L

The EQ-5D-5L assesses an adult patient's health status in a standardized way, is widely used in multiple diseases, and consists of 2 parts:

- EQ-5D-5L descriptive system
- EuroQol Quality of Life Scale – Visual Analog Scale (EQ-VAS).

The mean EQ-5D-5L health utility scores at baseline were lower than the US and UK general population scores (US: 0.71 vs 0.85, UK: 0.76 vs 0.86), indicating significant health-related quality of life impairment before exa-cel infusion.[99, 100] Clinically meaningful improvements in EQ-5D-5L were observed from Month 6 onward, with the mean (SD) increase from baseline at 2 years after infusion of US and UK index scores of 0.23 (0.20) points and 0.19 (0.18) points, respectively (Table 15). Any increase ≥ 0.078 (US) and ≥ 0.08 (UK) is considered clinically meaningful (the MCID).[101] These results indicate an impressive improvement in overall health status after exa-cel infusion, even exceeding general population norms, that was sustained through follow-up.

EQ visual analog scale (VAS) scores demonstrated substantial improvement at Month 6 onward, with the mean (SD) increase from baseline at 2 years after infusion of 28.3 (16.2) points, far exceeding the MCID for EQ VAS of 7 to 10 points, indicating early and meaningful improvement in patients' self-rated health status.[102]

Table 15: Results of EQ-5D-5L over Time (Study 121, PES at IA2)

PRO, Mean (SD)	Baseline n=17	Change at Month 6 n=16	Change at Month 12 n=17	Change at Month 18 n=16	Change at Month 24 n=8	MCID
EQ VAS	63.5 (22.5)	24.3 (27.1)	25.3 (23.2)	30.3 (25.5)	28.3 (16.2)	7–10 points
US Index Score	0.71* (0.23)	0.13 (0.23)	0.13 (0.22)	0.18 (0.21)	0.23 (0.20)	0.078
UK Index Score	0.76* (0.19)	0.10 (0.19)	0.11 (0.17)	0.14 (0.17)	0.19 (0.18)	0.08

IA2=second prespecified interim analysis with data cutoff date of 10 February 2023; MCID=minimal clinically important difference; n=size of subsample; PES=Primary Efficacy Set; PRO=patient-reported outcome.
Note: Shaded cells represent domains that met or exceeded MCID.
* Population norms are 0.85 for US and 0.86 for UK.

FACT-BMT

The FACT-BMT is commonly used in adult patients undergoing bone marrow transplantation and is a self-report questionnaire that includes two components:

- FACT-General (FACT-G) measures general physical, social, family, emotional, and functional well-being
- Bone marrow transplantation subscale (BMTS) measures treatment-specific concerns of bone marrow transplantation.

For both components, higher values indicate better quality of life.

FACT-BMT total scores demonstrated substantial improvement as early as Month 6, with the greatest mean (SD) increase from baseline occurring 2 years after exa-cel infusion: increase of 33.6 (16.7) points, indicating robust improvement in general well-being and quality of life that were sustained through follow-up.

On the FACT-G, improvement was observed in all four subscales, including physical, social/family, emotional, and functional well-being. Starting at 6 months after exa-cel infusion, overall scores far exceeded the MCID of 3 to 7 points (Table 16).[98, 103-105] The mean (SD) change from baseline for FACT-G was 29.8 (17.2) points at 2 years after exa-cel infusion.

The BMTS score also improved, with change in baseline exceeding the MCID of 2 to 3 points starting at Month 6, indicating clinically meaningful improvement in transplantation-related well-being.[105, 106] The mean (SD) increase from baseline for BMTS was 3.9 (5.7) points at 2 years after exa-cel infusion.

Table 16: Change in PRO Scores over Time on FACT-G, BMTS, and FACT-BMT (Study 121, PES at IA2)

PRO, Mean (SD)	Baseline n=17	Change at Month 6 n=16	Change at Month 12 n=17	Change at Month 18 n=16	Change at Month 24 n=8	MCID
FACT-G Total Score	67.5 (18.3)	16.5 (17.4)	20.5 (18.0)	21.8 (22.3)	29.8 (17.2)	3–7 points
BMTS	26.1(3.5)	3.6 (6.2)	5.3 (4.5)	5.4 (5.1)	3.9 (5.7)	2–3 points
FACT-BMT	93.6 (19.5)	20.0 (21.9)	25.8 (20.4)	27.2 (26.0)	33.6 (16.7)	–

BMTS= bone marrow transplantation subscale; FACT-BMT=Functional Assessment of Cancer Therapy – Bone Marrow Transplant; FACT-G=Functional Assessment of Cancer Therapy – General; IA2=second prespecified interim analysis with data cutoff date of 10 February 2023; MCID=minimal clinically important difference; n=size of subsample; PES=Primary Efficacy Set; PRO=patient-reported outcome.
Notes: Shaded cells represent domains that met or exceeded MCID.MCID not available for FACT-BMT total score.

ASCQ-Me

ASCQ-Me is a disease-specific health-related quality-of-life questionnaire that measures physical, mental, and social health, along with information on severity of disease in adult patients with SCD.

All ASCQ-Me subscales (emotional, social, stiffness, and sleep impact) improved more than the 5-point MCID at 2 years after infusion, indicating meaningful improvement in after treatment with exa-cel (Table 17). The mean (SD) increases from baseline at 2 years were: 17.7 (9.8) points for emotional, 23.8 (6.7) points for social functioning, 7.9 (12.9) points for stiffness, and 8.4 (8.3) points for sleep impact.

Additionally, the three ASCQ-Me pain-related subscale scores improved as early as Month 6 and continued to improve through 2 years. The mean (SD) changes from baseline for the pain-related subscales at 2 years were 10.9 (14.7) points for pain impact, -22.8 (8.2) points for pain-episode frequency, and -7.6 (15.2) points for pain-episode severity, compared with the MCID of 5 points for pain impact and -5 points for pain-episode frequency and pain-episode severity.

The level of impairment at baseline on these subscales indicates substantial disease burden of SCD in all domains measured within the ASCQ-Me. The improvements observed underscore the improvement in quality-of-life after treatment with exa-cel.

Table 17: Change in PRO Scores over Time on ASCQ-Me (Study 121, PES at IA2)

Category, Mean (SD)	Baseline n=17	Change at Month 6 n=16	Change at Month 12 n=17	Change at Month 18 n=16	Change at Month 24 n=8	MCID
Emotional Impact	50.2 (8.2)	9.5 (11.0)	10.2 (10.6)	10.1 (10.5)	17.7 (9.8)	5
Pain Impact	51.8 (9.5)	5.4 (9.8)	5.6 (9.6)	10.1 (9.8)	10.9 (14.7)	5
Social Functioning	47.0 (8.4)	11.0 (11.7)	15.6 (11.0)	15.6 (13.3)	23.8 (6.7)	5
Stiffness Impact	50.8 (8.5)	0.6 (13.1)	4.7 (10.9)	4.7 (8.7)	7.9 (12.9)	5

Category, Mean (SD)	Baseline n=17	Change at Month 6 n=16	Change at Month 12 n=17	Change at Month 18 n=16	Change at Month 24 n=8	MCID
Sleep Impact	45.3 (8.0)	4.8 (12.1)	4.3 (7.8)	2.9 (9.4)	8.4 (8.3)	5
Pain Episode Frequency	52.8 (6.5)	-14.6 (8.5)	-17.6 (8.1)	-19.7 (9.2)	-22.8 (8.2)	-5
Pain Episode Severity	53.8 (7.5)	-1.9 (11.9)	-1.4 (11.9)	-2.6 (12.1)	-7.6 (15.2)	-5

ASCQ-Me= Adult Sickle Cell Quality of Life Measurement System; IA2=second prespecified interim analysis with data cutoff date of 10 February 2023; MCID=minimal clinically important difference; n=size of subsample; PES=Primary Efficacy Set; PRO=patient-reported outcome.
Note: Shaded cells represent domains that met or exceeded MCID.

Pain NRS

Pain NRS is a measure of reporting intensity of pain in adults and adolescents. It is a commonly used instrument in healthcare that measures pain intensity on a 1-dimensional scale and is validated for use in adults and adolescents. Lower scores indicate improvement.

Clinically meaningful improvement in reported pain started around Month 12 and was sustained through 2 years: the mean (SD) change from baseline at 2 years after exa-cel infusion was -1.8 (3.1) points and exceeded the MCID of 1-point reduction from baseline.[107] At 2 years after exa-cel infusion, 75.0% of patients had a ≥ 1-point reduction in Pain NRS from baseline. As pain is a considerable aspect of the SCD patient experience, improvements in Pain NRS of this magnitude are particularly meaningful.[96, 108]

Conclusions from PROs

Overall, the PRO tools showed substantial and clinically meaningful improvements in scores over time that were sustained through 2 years of follow-up for adults with SCD. The magnitude of impact on the EQ-5D-5L is reflective of profound improvements in the quality of life for these patients who suffer from debilitating pain crises and substantial impairment of their abilities to perform activities of daily living. After exa-cel infusion, quality of life scores on the EQ-5D-5L VAS improved compared to baseline and exceed general population health utility score norms. These data are reinforced by the physical, social, and emotional sub-scales of the ASCQ-Me and FACT BMT. Improvements in the pain NRS and pain sub-scales of the ASCQ-Me provide additional context to the treatment benefits of exa-cel on alleviating SCD patients' overall pain experience and achieving VOC independence, while signifying the overall positive impact of treatment with exa-cel in this population.

7.2.10 Efficacy Analyses Supportive of HbF (%) as a Surrogate Efficacy Biomarker and VF9 As Intermediate Clinical Endpoint

During the pre-BLA meeting on 09 August 2022, FDA encouraged the Sponsor to put forward all data and justification in support of surrogate/intermediate endpoints that would predict clinical benefit at the time of the BLA submission. In this section, data are presented to demonstrate that in patients treated with exa-cel:

- HbF level ≥ 20% at Month 6 is a surrogate efficacy biomarker predictive of VOC-free for 12 consecutive months (VF12)
- VOC free for 9 consecutive months (VF9) is an intermediate clinical endpoint predictive of VOC-free for longer duration, including VOC-free for 12 consecutive months (VF12)

7.2.10.1 HbF (%) ≥20% at Month 6 as Surrogate Efficacy Biomarker Endpoint

Data from epidemiology, real-world evidence studies[7, 36, 109] and the exa-cel clinical data strongly support that achieving HbF (%) ≥ 20% results in > 90% likelihood of achieving VOC free for 12 consecutive months (VF12). Epidemiology data demonstrate that individuals with SCD-HPFH have little or no disease and are generally healthy, particularly those with HbF levels above 20%, in whom VOC events rarely, if ever, occur.[14, 27, 28] Evaluating HbF (%) ≥ 20% at the Month 6 time point after exa-cel infusion was selected because that is the time point that patients reach hematologic stability for HbF levels.

The association between HbF (%) levels and acute pain crises (similar to VOCs) was examined in the data from the Cooperative Study of Sickle Cell Disease (CSSCD), a real-world evidence study that enrolled individuals (including newborns) with SCD who had varying levels of HbF (Table 18). At HbF (%) of ≥ 20%, 92.9% of individuals were free of pain crises at 24 months, demonstrating that HbF (%) ≥ 20% is protective against VOCs.

Table 18: Proportion of Patient with HbF (%) ≥ 20% Who Are Pain Crisis Free at Month 24 (CSSCD)

Parameter, n (%)	Patients with HbF ≥ 20% N=127
Patients Free of Pain Crisis at Month 24	118 (92.9)

CSSCD=Cooperative Study of Sickle Cell Disease; HbF=fetal hemoglobin; N=total sample size; n=size of subsample.

Consistent with the natural history and real world data noted above, in Study 121 achieving HbF (%) ≥ 20% at Month 6 is predictive of clinical benefit where 29 of 30 (97%) patients in the PES that achieved the surrogate efficacy biomarker also achieved VF12 (Table 19).

Table 19: Summary of HbF (%) at 6 Months As Surrogate Biomarker Predictive of Primary Clinical Endpoint (VF12) (Study 121, PES)

	Primary Efficacy Set N=30	
HbF (%) at Month 6:	Achieved VF12	Did Not Achieve VF12
HbF (%) ≥ 20%*	29	1
HbF (%) < 20%	0	0

HbF=fetal hemoglobin; N=total sample size; PES=Primary Efficacy Set; VF12= not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion.
*Included two patients with intermittent missing HbF(%) at Month 6; Both had Month 5 and 9 HbF(%) data available and were ≥ 20%

In Study 121, the surrogate efficacy biomarker, HbF ≥ 20% at Month 6 was assessed in 41 patients who had been followed for at least 6 months. The patient who died due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel was excluded from the analyses, as their Month-6 HbF (%) data were diluted by frequent RBC transfusions while hospitalized, thus reducing the number to 40 patients. Of these 40 patients, 37 had Month 6 HbF (%) data available, and all of them were ≥ 20%. Three patients had missing Month 6 HbF (%) data:

- 2 patients had intermittent missing data at Month 6; both patients had Month 5 and Month 9 (and beyond) HbF (%) ≥ 20%; by interpolation, it was reasonable to assume both patients achieved Month 6 HbF (%) ≥ 20%.
- 1 patient had missing Month 6 data due to a late visit. The Month 3, 4 and 5 HbF (%) data were 42.6%, 57.9% and 61.3%, respectively. By extrapolation, it was reasonable to assume the patient will also achieved Month 6 HbF (%) ≥ 20%.

Overall, 40 of 40 (100%) patients achieved the surrogate efficacy biomarker of HbF ≥ 20% at Month 6.

7.2.10.2 VF9 as an Intermediate Clinical Endpoint

Per the FDA definition, an ICE is a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

Absence of VOCs for 9 consecutive months (VF9) represents a meaningful clinical benefit that is also reasonably likely to predict long-term efficacy. The testing of the second key secondary efficacy endpoint of VF9 was conducted as an intermediate clinical endpoint based on the EES.

Support for the use of VF9 as an intermediate clinical endpoint is derived from two real-world evidence studies (using Medicaid data and Center for International Blood and Marrow Transplant Research [CIBMTR] data[41]) from patients with SCD after allo-HSCT. These studies each demonstrated that VOC-free at 12 months (analogous to VF9 in Study 121) was predictive of VOC-free at 16 months and longer (analogous to VF12 in Study 121) in patients with SCD after allo-HSCT. Specifically, 91% (Medicaid) and 100% (CIBMTR) of patients who were VOC-free at 12 months were VOC-free at 16 months.

Consistent with the real world data noted above, in Study 121 (PES) achieving VF9 is predictive of clinical benefit where 29 of 29 patients that achieved VF9 also achieved VF12, and 1 patient that did not achieve VF9 also did not achieve VF12 (Table 20).

In Study 121, 31 of 32 (97%) patients in EES achieved the intermediate clinical endpoint of VF9.

Table 20: Summary of VF9 As Intermediate Clinical Endpoint Predictive of Primary Clinical Endpoint (VF12) (Study 121, PES)

	Primary Efficacy Set N=30	
VF9	**Achieved VF12**	**Did Not Achieve VF12**
Achieved VF9	29	0
Did Not Achieve VF9	0	1

EAC=endpoint adjudication committee; N=total sample size; PES=Primary Efficacy Set; RBC=red blood cell; SCD=sickle cell disease; VF9=absence of any severe VOCs for ≥9 consecutive months after exa-cel infusion; VF12= not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion; VOC=vaso-occlusive crisis.
Notes: The evaluation of VF9 started 60 days after last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The prohibited medication treatment period was excluded from the VOC-free duration. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.

7.2.11 Efficacy in Subgroups

Efficacy in Adolescents

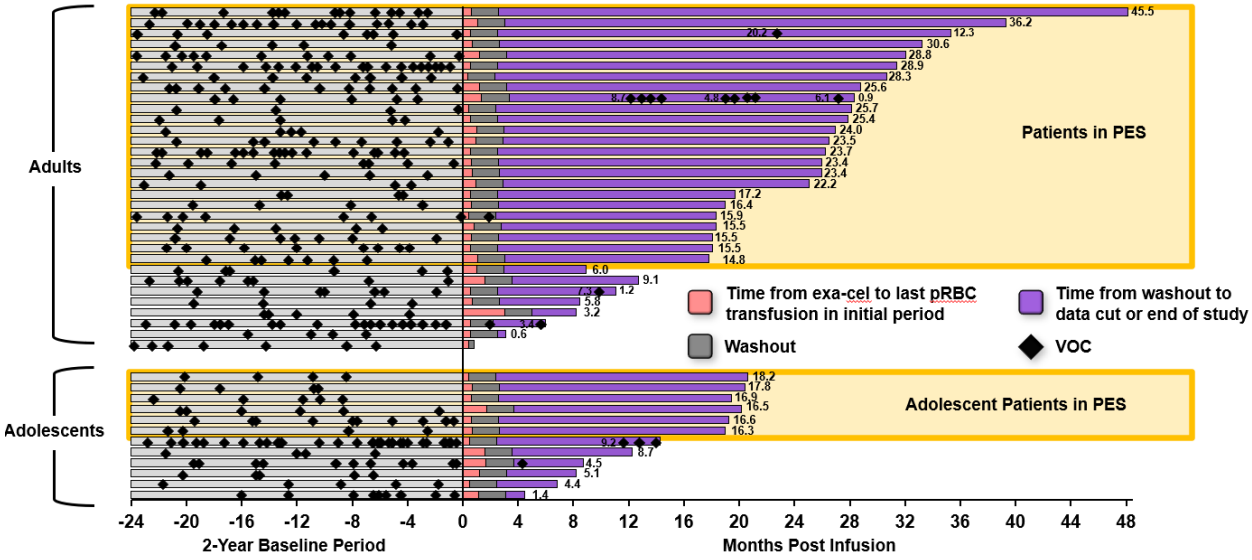
At the time of the updated 14 June 2023 data cutoff date, adolescent patients composed 12 of 44 (27.3%) patients in the FAS, 6 of 30 (20.0%) patients in the PES, and 7 of 32 (21.9%) patients in the EES (Section 7.2.2; Table 9).

As anticipated, based on the similarity of the pathophysiology across age groups and because the MOA is independent of age, the overall benefits observed in adolescent patients were similar to those observed in adults (Figure 16). Specifically,

- 6 of 6 (100%) adolescent patients in the PES achieved VF12 and HF12 and have been VOC free for up to 18.2 months (starting 60 days after the last RBC transfusion.
- 7 of 7 (100%) adolescent patients in the EES achieved VF9, which can be considered an intermediate clinical endpoint that predicts these patients will achieve VF12.
- 11 of 11 (100%) adolescent patients with at least 6 months of follow-up achieved HbF (%) ≥ 20%, which can be considered as a surrogate biomarker that reasonably likely predicts these patients will achieve VF12.

Two adolescent patients who were not yet eligible for the PES had VOCs after exa-cel infusion. Details are provided in Section 7.2.5.3.2.

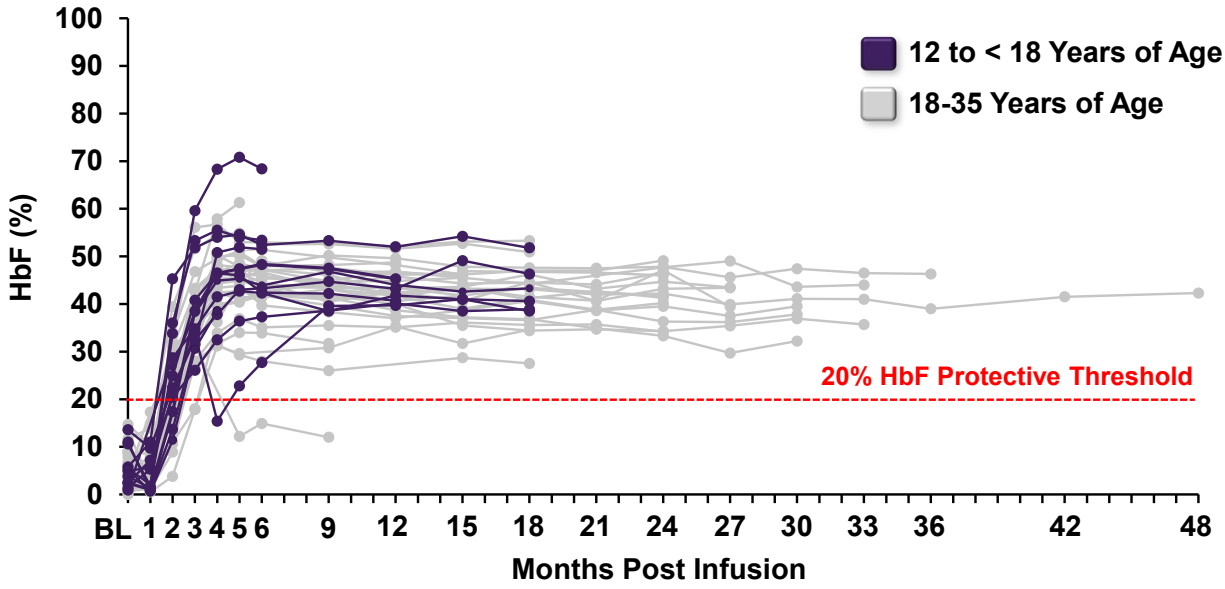
Figure 16: Duration of Severe VOC-Free Period for Individual Adolescent and Adult Patients (Studies 121 and 131, [SCD]FAS)



EAC=Endpoint Adjudication Committee; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; SCD=sickle cell disease; PES=Primary Efficacy Set; RBC=red blood cell; VOC=vaso-occlusive crisis.
Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria were included. Severe VOC-free duration starts 60 days after the last RBC transfusion for post-transplant support or SCD management and this duration is indicated by the numbers to the right of the purple bars. The RBC washout period refers to the duration of 60 days after the last RBC transfusion for post-transplant support or SCD management.

Moreover, all adolescent patients with at least 6 months of follow-up (N=11), had rapid, robust, and durable increases in levels of HbF (%) of ≥ 20% at Month 6 that were consistent with adult responses and sustained until data cutoff date (Figure 17).

Figure 17: Summary of HbF (%) over Time in Individual Adolescent and Adult Patients (Studies 121 and 131 [SCD]FAS)



BL=baseline; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; HbF=fetal hemoglobin; SAE=serious adverse event; SCD=sickle cell disease; VF12=not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion; VOC=vaso-occlusive crisis.
Note: Dashed red line=20% threshold for protection against disease complications. One patient (showed as the line with a dip at Month 4) had an exchange transfusion just before Month 4 for an SAE unrelated to exa-cel or SCD (vision blurred). Baseline was defined as the most recent non missing measurement collected before the start of mobilization in Study 121. One patient died due to respiratory failure from COVID-19 that was deemed unrelated to exa-cel. This patient had repeated transfusions from Study Day 115 through 265 while hospitalized and on extracorporeal membrane oxygenation, affecting the observed HbF (%) from Month 5 through Month 9.

Additional Subgroup Analyses

Comprehensive subgroup analyses were performed on the [SCD]PES for the primary (VF12) and key secondary (HF12) endpoints. Demographics and baseline medical characteristics investigated included age at screening, genotype, sex, VOC History, and race (Table 21).

Results of these analyses showed consistent and robust response to exa-cel, demonstrating that the exa-cel MOA works independently of age, genotype, sex, VOC history, and race, and offers transformational clinical outcomes across subgroups.

Table 21: Subgroup Analysis: Proportion of Patients Who Achieved VF12 or HF12 by Age, Genotype, Sex, VOC History, and Race (Studies 121 and 131 [SCD]PES)

Subgroup, n (%); (95% CI)	VF12 N=30	HF12 N=30
Age		
Adolescents (12-<18 years of age) (n=6)	6 (100); (54.1, 100)	6 (100); (54.1, 100)
Adults (18-35 years of age), (n=24)	23 (95.8); (78.9, 99.9)	24 (100); (85.8, 100)
Genotype		

Subgroup, n (%); (95% CI)	VF12 N=30	HF12 N=30
β^s/β^s, n=29	28 (96.6); (82.2, 99.9)	29 (100); (88.1, 100)
non-β^s/β^s, n=1	1 (100); (–, –)	1 (100) (–, –)
Sex		
Male, n=16	16 (100); (79.4, 100)	16 (100); (79.4, 100)
Female, n=14	13 (92.9); (66.1, 99.8)	14 (100); (76.8, 100)
VOC history		
≥ 3 VOCs/year for 2 years prior at baseline, n=17	16 (94.1); (71.3, 99.9)	17 (100); (80.5, 100)
Race		
Black or African American, n=26	25 (96.2); (80.4, 99.9)	26 (100); (86.8, 100)
Other, n=4	4 (100) (–, –)	4 (100) (–, –)

exa-cel=exagamglogene autotemcel; HbF=fetal hemoglobin; HF12=free from in-patient hospitalization for VOC events for at least 12 consecutive months after exa-cel infusion; N=total sample size; n=size of subsample; PES=Primary Efficacy Set; SCD=sickle cell disease; VF12=not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion; VOC=vaso-occlusive crisis.

7.3 Efficacy Conclusions in Sickle Cell Disease

Exa-cel is designed to be a one-time treatment, leading to a functional cure in patients with SCD.

In the pivotal clinical study (Study 121), exa-cel has been shown to reactivate HbF production to levels known to eliminate disease complications consistent with individuals with SCD who co-inherit HPFH (Section 3.3). As anticipated based on the MOA, the consistency of editing translates into long-term durability of effect that is observed after treatment with exa-cel. Treatment with exa-cel consistently resulted in rapid, robust, and durable increases in HbF levels, which were maintained through Study 131.

As discussed in Section 7.2, all evaluated efficacy endpoints demonstrate maintenance of long-term benefit from exa-cel treatment. Efficacy was observed early and maintained through all subsequent follow-up (Month 48).

Specifically:

- The pivotal Study 121 and long-term follow-up Study 131 showed transformational clinical benefit in adults and adolescents:
    - 29 of 30 (96.7%) patients in the PES achieved VF12, including 6 adolescent patients;
    - 30 of 30 (100%) patients in the PES achieved HF12, including 6 adolescent patients;
    - 40 of 40 (100%) patients achieved the surrogate efficacy biomarker of HbF ≥ 20% at Month 6, including 11 adolescent patients;
    - 31 of 32 (97%) patients achieved the intermediate clinical endpoint (ICE), VF9 including 7 adolescent patients.
- Adolescents (ages 12 to 17 years) comprised ~30% of the total population (n=11). Transformational clinical benefit was consistent between adolescents and adults.

- Twenty-eight of 29 (96.6%) SCD patients who achieved VF12 have remained VOC free. The mean (SD) VOC free duration was 22.4 (7.2) months, ranging up to 41.1 months.
- The mean HbF (%) levels were maintained at approximately ≥40% and mean total Hb levels were maintained at ≥11.1 g/dL from Month 6 through the duration of follow-up. In addition, prediction analyses via modeling further support the expected extended durability of HbF with all patients predicted to have HbF ≥20%, a level that has been shown to be associated with absence of VOCs.
- High stable levels of allelic editing in peripheral blood and $CD34^+$ cells of the bone marrow were achieved early and maintained, demonstrate durability of the engrafted cells.

Benefits of exa-cel treatment also translate into long-term benefits in other secondary endpoints that also show improvements, including improvements in markers of hemolysis (LDH and haptoglobin) and in PROs. The markers of hemolysis and PROs will continue to be measured in the 15-year follow-up Study 131.

By eliminating VOCs for patients with SCD, exa-cel treatment is expected to modify the long-term course of disease by reducing end organ damage and ultimately improving overall survival.

In summary, the totality of exa-cel efficacy shows overwhelming and transformational clinical benefit following exa-cel treatment, supports the proposed indication, and addresses the significant unmet need for a curative treatment for patients with SCD.

8 CLINICAL SAFETY IN SICKLE CELL DISEASE

Summary

- A total of 46 patients have received exa-cel infusion in Study 121; this reflects all patients planned to dose in the study.
- 44 patients had received exa-cel infusion at the time of data cutoff, with a mean (SD) of 20.3 (10.4) and median (range) follow-up of 19.3 (0.8, 48.1) months after infusion and a cumulative 73.5 patient-years follow-up
- Adverse events (AEs) were consistent with the use of busulfan myeloablative conditioning, HSCT, and underlying disease:
  - The most common adverse events were nausea (70.5%), stomatitis (63.6%), vomiting (56.8%), and febrile neutropenia (54.5%)
  - Most AEs, Grade 3/4 AEs and SAEs occurred within he first 3 to 6 months after myeloablative conditioning and exa-cel infusion and decreased thereafter
  - No SAEs were considered related or possibly related to exa-cel
  - There were no clinically significant infusion-related reactions
- The safety profile was consistent in adolescents (ages 12 to 17 years) and adults (ages ≥ 18 years)
- All (100%) patients successfully achieved both neutrophil and platelet engraftment, with no patients experiencing graft failure or graft rejection.
- The time to platelet engraftment is longer than that reported in the allo-HSCT literature and delayed platelet engraftment is considered a potential risk for exa-cel.
- There have been no reports of hematologic malignancies in patients treated with exa-cel. There is a known risk of malignancy following busulfan and HSCT. However, there is no evidence from extensive non-clinical investigations of additional risk of hematologic malignancy from exa-cel treatment.

8.1 Treatment Exposure and Mobilization

In the exa-cel development program for SCD, all 46 severe SCD patients in Study 121 who were planned to be dosed have been dosed. The 44 patients who have received exa-cel as of the 14 June 2023 data cutoff date received exa-cel at a median dose (range) of 4.0 (2.9, 14.4) × 106 CD34+ cells/kg. The mean (SD) of 20.3 (10.4) and median (range) follow-up duration after exa-cel infusion were 19.3 (0.8, 48.1) months, which corresponds to 73.5 patient--years of exposure after exa-cel infusion (Table 22).

Table 22: Patient Exposure to Exa-cel and Duration of Follow-up (Studies 121 and 131, [SCD]FAS)

Parameter	[SCD]FAS N=44
Follow-up duration after exa-cel infusion (month)	
Mean (SD)	20.1 (10.4)
Median (min, max)	19.3 (0.8, 48.1)
Exposure after exa-cel infusion (patient-months)	882.4
Exposure after exa-cel infusion (patient-years)	73.5

Parameter	[SCD]FAS N=44
Follow-up duration after exa-cel infusion by interval[a], n (%)	
≤ 3 months	1 (2.3)
> 3 months to ≤ 6 months	2 (4.5)
> 6 months to ≤ 1 year	8 (18.2)
> 1 year to ≤ 2 years	16 (36.4)
> 2 years[a]	17 (38.6)
≥ 18 months[b]	30 (68.2)

Exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; SCD=sickle cell disease.
a. Follow-up duration is not equivalent to study visit. Due to protocol-specified visit windows, a patient in this category may not have completed the Month 24 Visit in Study 121, as applicable, thus had not enrolled in Study 131.
b. Includes 1 patient who was 6 days prior to 18 months of follow-up at the time of the data cutoff date.

8.2 Adverse Events

Exa-cel's safety profile is consistent with AEs related to myeloablative busulfan conditioning[84], HSCT, and underlying disease[10] (Table 23). Clinical findings are supported by extensive nonclinical investigations for potential toxicities or off-target edits, none of which were identified in nonclinical studies (Section 5).

Table 23: Overview of Adverse Events From Exa-cel Infusion through 2 Years of Follow-up (Study 121, FAS)

Patients with, n (%)	FAS N=44
Any AE	44 (100)
Any AE related or possibly related to exa-cel	13 (29.5)
Any AE related or possibly related to busulfan	44 (100)
Grade 3/4 AE	42 (95.5)
SAE	20 (45.5)
SAE related or possibly related to exa-cel	0
SAE related or possibly related to busulfan	4 (9.1)
AE leading to study discontinuation	0
AE leading to death	1 (2.3)[a]

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; SAE=serious adverse event; SAS=Safety Analysis Set.
a. One patient died due to COVID-19 infection that resulted in respiratory failure, not related to exa-cel; this resulted in study discontinuation.

8.2.1 Common Adverse Events

The most common AEs (occurring in ≥ 40% of patients) after myeloablative busulfan conditioning and exa-cel infusion were nausea, stomatitis, vomiting, febrile neutropenia,

abdominal pain, headache, pruritus, decreased appetite, platelet count decreased, constipation, pain in extremity, arthralgia, and pyrexia (Table 24).

Table 24: Common Adverse Events Occurring in ≥ 25% of Patients From Exa-cel Infusion through 2 Years of Follow-up (Study 121, FAS)

Preferred Term[a], n (%)	FAS N=44
Patients with any AE	44 (100)
Nausea	31 (70.5)
Stomatitis	28 (63.6)
Vomiting	25 (56.8)
Febrile neutropenia	24 (54.5)
Abdominal pain	22 (50.0)
Headache	22 (50.0)
Pruritus	22 (50.0)
Decreased appetite	21 (47.7)
Platelet count decreased	21 (47.7)
Constipation	20 (45.5)
Pain in extremity	20 (45.5)
Arthralgia	19 (43.2)
Pyrexia	18 (40.9)
Diarrhea	17 (38.6)
Neutrophil count decreased	17 (38.6)
Anemia	16 (36.4)
Fatigue	16 (36.4)
Mucosal inflammation	16 (36.4)
Skin hyperpigmentation	16 (36.4)
Back pain	15 (34.1)
Hypokalemia	15 (34.1)
Neutropenia	13 (29.5)
Edema peripheral	12 (27.3)
Thrombocytopenia	12 (27.3)
Abdominal pain upper	11 (25.0)
Alanine aminotransferase increased	11 (25.0)
COVID-19	11 (25.0)
Gastritis	11 (25.0)
Pain	11 (25.0)

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; n=size of subsample.
a. All preferred-term events are described in busulfan product information by matching term or similar medical concept (Otsuka 2015).

8.2.2 Treatment-Related Adverse Events

All AEs considered by the investigator as possibly related or related to exa-cel that occurred in ≥ 2 patients were laboratory-related events (CD4 lymphocyte decreased, lymphopenia, and neutropenia) (Table 25). All AEs considered possibly related or related to exa-cel were also considered possibly related or related to busulfan, except for one nonserious AE of neutropenia, which was considered possibly related or related to exa-cel only.

Table 25: Adverse Events Related or Possibly Related to Exa-cel From Exa-cel Infusion through 2 Years of Follow-up (Study 121, FAS)

Preferred Term, n (%)	FAS N=44
Patients with any AE related to exa-cel[a]	13 (29.5)
CD4 lymphocytes decreased	8 (18.2)
Lymphopenia	5 (11.4)
Neutropenia	2 (4.5)
Dermatitis	1 (2.3)
Platelet count decreased	1 (2.3)
Thrombocytopenia	1 (2.3)

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; n=size of subsample.
a. "Related", "Possibly Related", and "Missing" are considered as related.

8.2.3 Time to Onset of Adverse Events after Exa-cel Treatment

Overall, the type of AEs and timing of onset were consistent with busulfan myeloablative conditioning and the peri-transplant period. No new trends or patterns associated with exa-cel were observed (Table 26). Across all intervals, most AEs were non-serious and Grade 1 or 2 in severity. The majority (> 70%) of AEs, serious adverse events (SAEs), and Grade 3/4 AEs occurred during the first 6 months after exa-cel infusion. None of the SAEs that occurred ≥ 6 months after exa-cel infusion were considered related or possibly related to busulfan. No SAEs were considered related or possibly related to exa-cel during any time interval.

Table 26: Adverse Events by Onset Time Interval From Exa-cel Infusion (Study 121, FAS)

Category	Infusion to < 6 Months N=44	6 to < 12 Months N=41	12 to < 18 Months N=33	≥ 18 Months N=29
Patients with any AE, n (%)	44 (100.0)	29 (70.7)	22 (66.7)	16 (55.2)
Total number of AEs	1554	209	121	64
Patients with Grade 3/4 AE, n (%)	42 (95.5)	9 (22.0)	7 (21.2)	3 (10.3)
Number of Grade 3/4 AEs	364	32	11	8
Patients with SAE, n (%)	15 (34.1)	8 (19.5)	3 (9.1)	3 (10.3)
Number of SAEs	46	13	3	4

Category	Infusion to < 6 Months N=44	6 to < 12 Months N=41	12 to < 18 Months N=33	≥ 18 Months N=29
Time-Adjusted AE Rates (Events/Patient-Months)				
All AEs	6.141	0.963	0.661	0.541
AEs related to exa-cel	0.087	0.009	0.005	0
Grade 3/4 AEs	1.438	0.147	0.060	0.068
SAEs	0.182	0.060	0.016	0.034
SAEs related to exa-cel	0	0	0	0

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; n=size of subsample; SAE=serious adverse event.
Notes: Any AEs missing relationship to exa-cel were counted as related to exa-cel.

8.2.4 Grade ≥ 3 Adverse Events

Most patients (42 of 44 [95.5%]) had at least 1 AE with a maximum severity of Grade ≥ 3 (Table 27). However, Grade ≥ 3 AEs reported in Study 121 were consistent with the use of busulfan for myeloablative conditioning (e.g., cytopenias, stomatitis, and mucosal inflammation)[84] or associated with underlying disease (e.g., cholelithiasis).[110, 111] Seven (15.9%) patients had a Grade ≥ 3 AE considered related or possibly related to exa-cel, while 42 (95.5%) had a Grade ≥ 3 AEs considered related or possibly related to busulfan.

Additionally, most Grade ≥ 3 AEs occurred within 6 months of exa-cel infusion and myeloablative conditioning (Section 8.2.3; Table 26).

Table 27: Grade ≥ 3 Adverse Events Occurring in ≥ 10% of Patients From Exa-cel Infusion through 2 Years of Follow-up (Study 121, FAS)

Preferred Term, n (%)	FAS N=44
Patients with any Grade ≥ 3 AE	42 (95.5)
Stomatitis	24 (54.5)
Febrile neutropenia	21 (47.7)
Platelet count decreased	21 (47.7)
Decreased appetite	18 (40.9)
Neutrophil count decreased	17 (38.6)
Mucosal inflammation	14 (31.8)
Anemia	11 (25.0)
Thrombocytopenia	11 (25.0)
Neutropenia	10 (22.7)
White blood cell count decreased	6 (13.6)
Abdominal pain	5 (11.4)
CD4 lymphocytes decreased	5 (11.4)
Cholelithiasis	5 (11.4)

Preferred Term, n (%)	FAS N=44
Pruritus	5 (11.4)

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; n=size of subsample.

8.2.5 Serious Adverse Events

After exa-cel infusion, 20 (45.5%) patients had at least 1 SAE (Table 28). No SAEs were reported as possibly related or related to exa-cel (Table 4), and all SAEs reported are either described in the busulfan product information[84] by matching PT or similar medical concept, or are associated with underlying disease (e.g., cholelithiasis, sickle cell anemia with crisis).[12, 110-112]

Table 28: Serious Adverse Events Occurring in ≥ 2 Patients From Exa-cel Infusion through 2 Years of Follow-up (Study 121, FAS)

Preferred Term[a], n (%)	FAS N=44
Patients with any SAE	20 (45.5)
Cholelithiasis	4 (9.1)
Pneumonia	4 (9.1)
Abdominal pain	3 (6.8)
Constipation	3 (6.8)
Pyrexia	3 (6.8)
Sickle cell anemia with crisis	3 (6.8)[b]
Abdominal pain upper	2 (4.5)
Non-cardiac chest pain	2 (4.5)
Oropharyngeal pain	2 (4.5)
Pain	2 (4.5)
Sepsis	2 (4.5)

Exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; PT=Preferred Term; N=total sample size; n=size of subsample; SAE=serious adverse event; VOC: vaso-occlusive crisis.
a. All PTs are either described in the busulfan product information by matching PT or similar medical concept or are associated with underlying disease (cholelithiasis, sickle cell anemia with crisis).
b. Corresponds to hospitalizations for VOCs in three patients.

8.3 Deaths

One adult patient in Study 121 died of respiratory failure due to complications from COVID-19 infection. The event was considered not related to exa-cel and possibly related to busulfan. A narrative is provided in Appendix 11.2.1. No other deaths have occurred across the exa-cel program.

8.4 Engraftment

8.4.1 Neutrophil Engraftment and Neutrophil Recovery

Neutrophil engraftment was defined as the first day of 3 consecutive measurements of absolute neutrophil count (ANC) ≥ 500/μL on 3 different days, achieved within 42 days after exa-cel infusion (Study Day 43), without use of unmodified $CD34^+$ cells after reaching the nadir, defined as ANC < 500/μL. Engraftment failure was defined as not achieving neutrophil engraftment by 42 days after exa-cel infusion (Study Day 43) or having to receive backup $CD34^+$ stem cells at any time during the period of neutropenia.

All 44 patients (100%) who completed busulfan conditioning and received exa-cel achieved neutrophil engraftment by Study Day 43, and no patients required back-up $CD34^+$ cells (Table 29).

The Kaplan-Meier plot for time to neutrophil engraftment is provided in Figure 18.

The median (range) time to neutrophil engraftment was 27.0 (15, 40) days (Table 29). Within 2 months after exa-cel infusion, median neutrophil counts further increased and remained ≥ 1.5 × 109/L (Figure 19), which is Grade 1 or normal, per Common Terminology Criteria for Adverse Events (CTCAE).

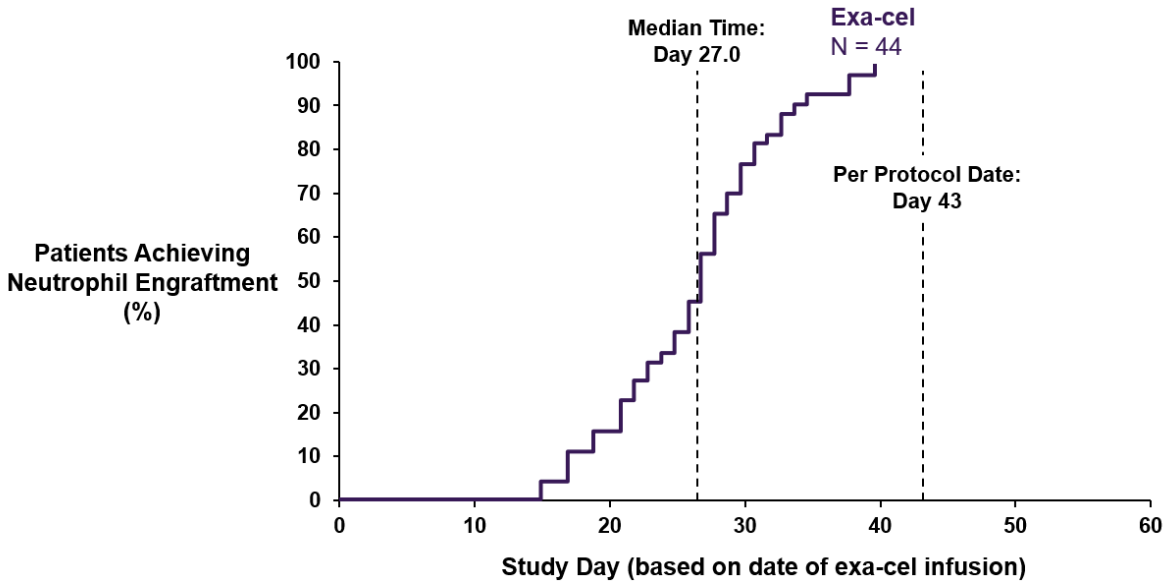
Relative to allo-HSCT, the median time to neutrophil engraftment with exa-cel is comparable to the times reported in allo-HSCT[56, 113-115] and aligns with those seen with other genetic therapies involving HSCT[73] (see Table 37 in Appendix 11.2.2 for detailed information on reference ranges). There was no association between infection AEs or SAEs and neutrophil engraftment times.

Table 29: Summary of Neutrophil Engraftment (Study 121, FAS)

Parameter	FAS N=44
Patients who achieved neutrophil engraftment n (%)	44 (100)
Time to neutrophil engraftment, days[a]	
Mean (SD)	26.5 (6.1)
Median (min, max)	27.0 (15, 40)

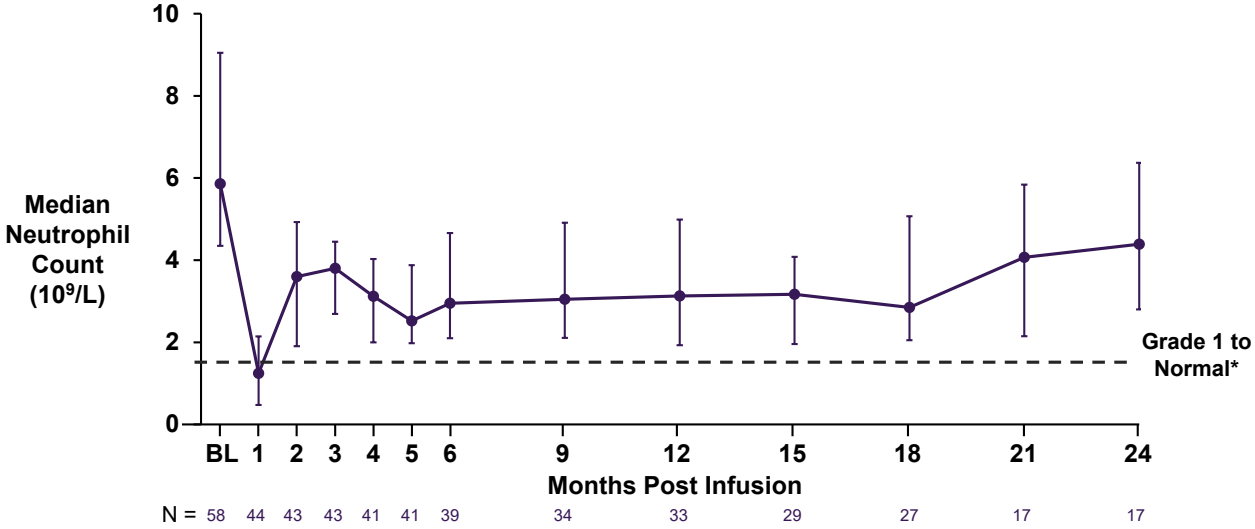
FAS=Full Analysis Set; N=total sample size; n=size of subsample.
Notes: Neutrophil engraftment was defined as the first day of 3 consecutive measurements of absolute neutrophil count ≥ 500/μL on 3 different days without use of the unmodified $CD34^+$ cells after reaching a nadir of absolute neutrophil count < 500/μL.

Figure 18: Kaplan-Meier Plot for Time to Neutrophil Engraftment (Study 121, FAS)



FAS=Full Analysis Set; N=total sample size.
Note: Neutrophil engraftment was defined as the first day of 3 consecutive measurements of absolute neutrophil count ≥ 500/μL on 3 different days, without the use of the unmodified $CD34^+$ cells after reaching the nadir, defined as absolute neutrophil count < 500/μL achieved within 42 days after exa-cel infusion (Study Day 43). Exa-cel infusion was Study Day 1.

Figure 19: Median Neutrophil Counts over Time (Study 121, SAS)



N=total sample size; PBMC=peripheral blood mononuclear cell; SAS=Safety Analysis Set.
Note: Analysis was performed on the Safety Analysis Set (N=58), which includes all patients who started the mobilization regimen. Mobilization started with subcutaneous plerixafor 2-to-3 hours before the start of apheresis to collect PBMCs. First and third quartile values are plotted as bars at each visit. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of the first mobilization.
* Common Terminology Criteria for Adverse Events (CTCAE): 1.5 × 10^9/L to < lower limit of normal.

8.4.2 Platelet Engraftment and Platelet Recovery

Platelet engraftment was defined as the first of 3 consecutive measurements on 3 separate days with ≥ 50,000 platelets/μL without a platelet transfusion for 7 consecutive days. For patients discharged early, platelet engraftment was defined per protocol as Day 7 after the last platelet transfusion if the next 3 platelet counts were consecutively ≥ 50,000/μL without platelet transfusion support. This approach is consistent with transplant guidance and the HSCT field in context of less frequent platelet testing, as would be the case after hospital discharge.

Of the 44 patients who achieved neutrophil engraftment, 43 (97.7%) also achieved platelet engraftment as of the 14 June 2023 data cutoff date. One patient was at Study Day 24 and pending platelet engraftment at the time of the data cutoff date. After the 14 June 2023 data cutoff date, the patient subsequently achieved platelet engraftment on Study Day 26 (Table 30).

The median (range) time to platelet engraftment was 35.0 (23 to 126) days (N=43; Table 30).

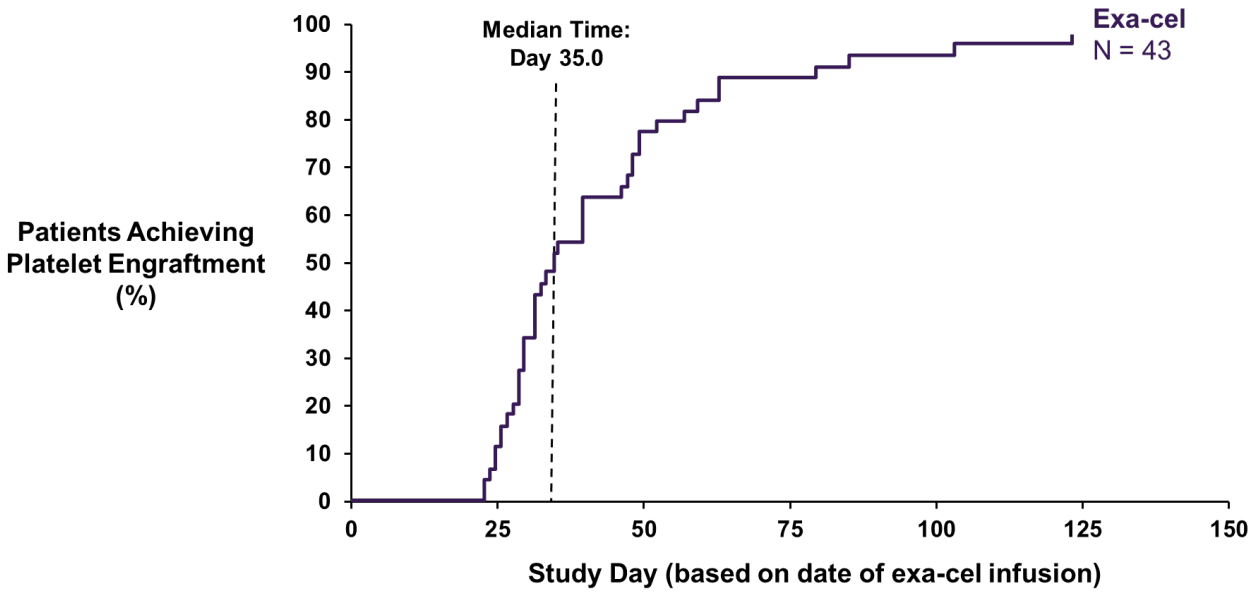
The Kaplan-Meier plot for time to platelet engraftment is provided in Figure 20.

Table 30: Summary of Platelet Engraftment (Study 121, FAS)

Time to Platelet Engraftment (Days)	FAS N=44
Patients who achieved platelet engraftment, n (%)	44 (100)[a]
Time to platelet engraftment[b]	
Mean (SD)	43.2 (22.2)
Median (min, max)	35.0 (23, 126)

FAS=Full Analysis Set; N=total sample size; n=size of subsample; PE=platelet engraftment.
a. One patient achieved platelet engraftment on Study Day 26, two days after the 14 June 2023 data cutoff date.
b. Times do not include the patient who achieved engraftment after the data cutoff date (on Study Day 26).
Notes: PE was defined as the first day of 3 consecutive measurements of unsupported (no platelet transfusions for the last 7 days) platelet ≥ 50,000/μL on 3 different days after exa-cel infusion after reaching nadir, defined as platelet < 50,000/μL, or the first platelet transfusion whichever is earlier. For patients who were discharged before reaching PE, PE was defined as the seventh day after the last platelet transfusion, if there were 3 subsequent and consecutive unsupported measurements of unsupported platelet ≥ 50,000/μL on 3 different days.

Figure 20: Kaplan-Meier Plot for Time to Platelet Engraftment (Study 121, FAS)



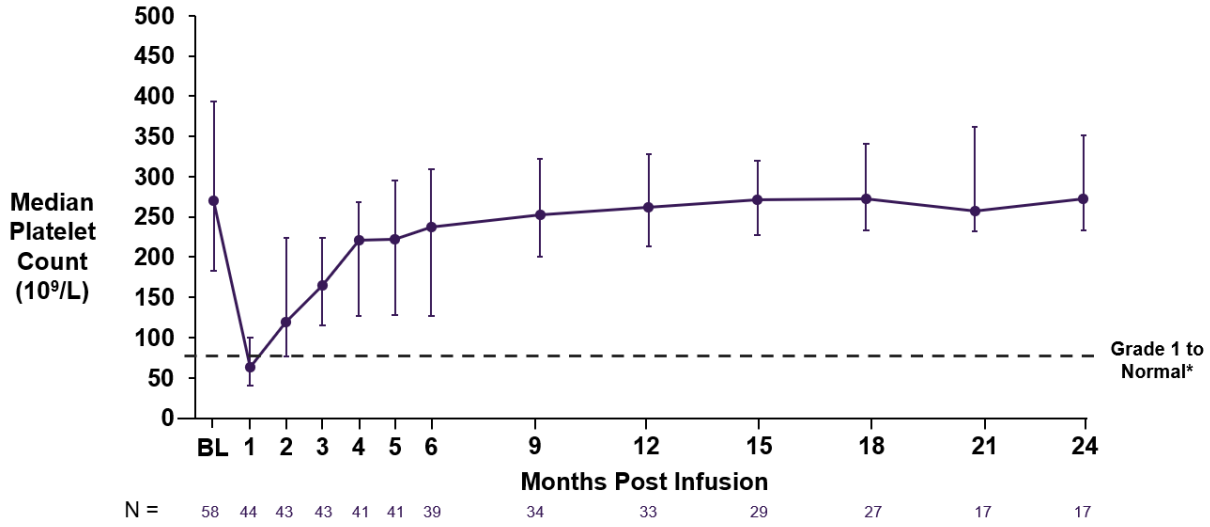
Exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set.
Notes: PE was defined as first of 3 consecutive measurements on 3 separate days with platelets ≥ 50,000/μL without a platelet transfusion for 7 consecutive days, after reaching the nadir (defined as platelet < 50,000/μL) or the first platelet transfusion, whichever is earlier. For patients discharged early, Day 7 after the last platelet transfusion was the day of PE, as long as 3 subsequent and consecutive unsupported measurements on 3 different days were ≥ 50,000/μL. This last platelet transfusion refers to the last platelet transfusion proceeding these 3 measurements. Exa-cel infusion was Study Day 1. One patient achieved platelet engraftment on Study Day 26, two days after the 14 June 2023 data cutoff date.

Overall platelet recovery was robust, as displayed in Figure 21, with the average platelet count > 100 × 10^9/L by Month 2 with further recovery thereafter to the normal range (>150 × 10^9/L) which was sustained through the duration of follow-up.

The median time to platelet engraftment is consistent with other genetic therapies for SCD: 36 days (range: 18, 136).[73] However the median time to platelet engraftment is longer than those reported in allo-HSCT literature: 19 to 28 days (range: 9, 232 days).[56, 113-116] See Table 37 in Appendix 11.2.2 for detailed information on reference ranges in the literature.

There was no association between time to platelet engraftment and the incidence of bleeding AEs and SAEs. Nonetheless, the potential for longer time to platelet engraftment is considered a potential risk and is included as part of the Pharmacovigilance Plan (Section 8.11).

Figure 21: Median Platelet Counts over Time (Study 121, SAS)



BL=baseline; N=total sample size; PBMC=peripheral blood mononuclear cell; SAS=Safety Analysis Set.
Notes: Analysis was performed on the Safety Analysis Set (N=58), which includes all patients who started the mobilization regimen. Mobilization started with subcutaneous plerixafor 2-to-3 hours before the start of apheresis to collect PBMCs. First and third quartile values are plotted as bars at each visit. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Error bars represent the 1st and 3rd quartiles around median.
* Common Terminology Criteria for Adverse Events (CTCAE): 75 × 10^9/L to < lower limit of normal.

8.5 Safety in Subgroups

Subgroup analyses of safety were performed for age, sex, race, genotype, and geographic region.

8.5.1 Safety in Adolescents and Adults

Adolescent patients (ages 12 to 17 years) were enrolled and treated once efficacy and safety had been shown in adults (ages 18 to 35 years). The median (range) follow-up for all adolescent and adult patients who received exa-cel infusion in the Study 121 and Study 131 FAS were 16.7 (4.5, 20.6) and 25.5 (0.8 to 48.1) months, respectively.

The observed safety profile was generally similar between adolescents (ages 12 to 17 years) and adults (Table 31). Across age groups, AEs were consistent with the use of busulfan for myeloablative conditioning, HSCT, and underlying disease. No differences attributed to exa-cel were identified in either age group. The incidences of AEs and SAEs after exa-cel infusion through 2 years of follow-up were generally similar for the two age groups.

Table 31: Summary of Adverse Events in Adolescent and Adult Participants, through 2 Years of Follow-up (Study 121, FAS)

	Age at Screening	
Adverse Events, n (%)	**12–<18 Years N=12**	**18-35 Years N=32**
Patients with any AE	12 (100)	32 (100)
AE related or possibly related to exa-cel	2 (16.7)	11 (34.4)
AE related or possibly related to busulfan	12 (100)	32 (100)
Grade 3/4 AE	10 (83.3)	32 (100)
SAE	5 (41.7)	15 (46.9)
SAE related or possibly related to exa-cel	0	0
SAE related or possibly related to busulfan	0	4 (12.5)
AE leading to study discontinuation	0	0
AE leading to death	0	1[a] (3.1)

AE=adverse event; exa-cel=exagamglogene autotemcel; FAS=Full Analysis Set; N=total sample size; n=size of subsample; SAE=serious adverse event;.
Notes: An AE missing relationship to busulfan/exa-cel is counted as related to busulfan/exa-cel.
a. Patient died of respiratory failure due to complications from COVID-19 that was considered unrelated to exa-cel.

The most common AEs were largely consistent between adolescent patients and adults, with several common AEs occurring with less frequency in adolescents as compared to adults (Table 32).

Table 32: Common Adverse Events Occurring in > 50% of Adolescent or Adult Participants, through 2 Years of Follow-up (Study 121, FAS)

	Age at Screening	
Preferred term, n (%)	**12–<18 Years N=12**	**18–35 Years N=32**
Nausea	8 (66.7)	23 (71.9)
Stomatitis	5 (41.7)	23 (71.9)
Febrile neutropenia	3 (25.0)	21 (65.6)
Vomiting	7 (58.3)	18 (56.3)
Abdominal pain	5 (41.7)	17 (53.1)
Decreased appetite	4 (33.3)	17 (53.1)
Platelet count decreased	4 (33.3)	17 (53.1)
Pruritus	7 (58.3)	15 (46.9)
Mucosal inflammation	7 (58.3)	9 (28.1)
Neutropenia	7 (58.3)	6 (18.8)

FAS=Full Analysis Set; N=total sample size; n=size of subsample.

Rates of SAEs among adolescents were also consistent with adults (Table 33). No SAE occurred in two or more adolescent participants.

Table 33: Serious Adverse Events Occurring in ≥ 2 Adolescent or Adult Participants, through 2 Years of Follow-up (Study 121, FAS)

	Age at Screening	
Preferred term, n (%)	**12–<18 Years N=12**	**18–35 Years N=32**
Patients with any SAE	5 (41.7)	15 (46.9)
Cholelithiasis	1 (8.3)	3 (9.4)
Pneumonia	1 (8.3)	3 (9.4)
Sickle cell anaemia with crisis	0	3 (9.4)
Abdominal pain	1 (8.3)	2 (6.3)
Constipation	1 (8.3)	2 (6.3)
Pain	0	2 (6.3)
Pyrexia	1 (8.3)	2 (6.3)
Sepsis	0	2 (6.3)

FAS=Full Analysis Set; N=total sample size; n=size of subsample; SAE=serious adverse event.

Rates of severe (Grade ≥ 3) AEs were generally consistent between adolescent and adult patients (Table 34).

Table 34: Grade ≥ 3 Adverse Events Occurring in ≥ 20% of Adolescent or Adult Participants, through 2 Years of Follow-up (Study 121, FAS)

	Age at Screening	
Preferred term, n (%)	**12–<18 Years N=12**	**18–35 Years N=32**
Patients with any Grade ≥ 3 AE	10 (83.3)	32 (100)
Stomatitis	3 (25.0)	21 (65.6)
Febrile neutropenia	1 (8.3)	20 (62.5)
Platelet count decreased	4 (33.3)	17 (53.1)
Decreased appetite	4 (33.3)	14 (43.8)
Neutrophil count decreased	3 (25.0)	14 (43.8)
Mucosal inflammation	6 (50.0)	8 (25.0)
Thrombocytopenia	4 (33.3)	7 (21.9)
Anaemia	5 (41.7)	6 (18.8)
Neutropenia	4 (33.3)	6 (18.8)

AE=adverse event; FAS=Full Analysis Set; N=total sample size; n=size of subsample.

Additionally, there were no clinically relevant differences in success of neutrophil or platelet engraftment or time to engraftment based on age (Table 35). As shown in Figure 22,

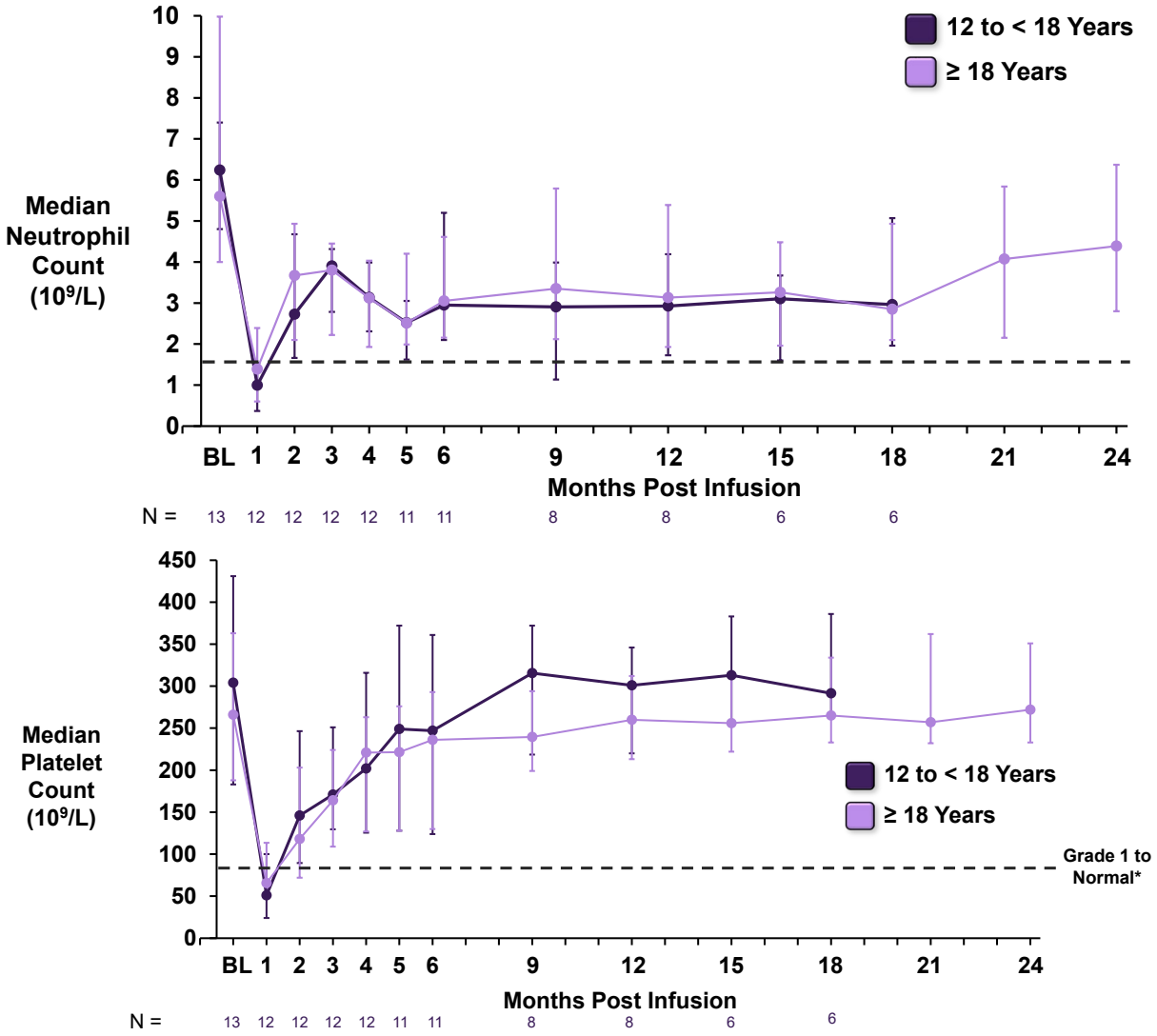
adolescents achieved and sustained increased neutrophil and platelet counts at consistent rates along similar timelines.

Table 35: Summary of Neutrophil and Platelet Engraftment in Adolescent and Adult Participants, through 2 Years of Follow-up (Study 121, FAS)

	Age at Screening	
Engraftment, days	**12–<18 Years N=12**	**18–35 Years N=32**
Neutrophil engraftment		
Mean	29.8	25.2
Median (range)	28.0 (24, 40)	25.5 (15, 38)
Platelet engraftment		
Mean	46.2	42.0[a]
Median (range)	44.5 (23, 81)	32.0 (23, 126)[a]

FAS=Full Analysis Set; N=total sample size.
Note: Adolescent patients were considered ages ≥ 12 to <18 years of age; adult patients were considered ages ≥ 18 to < 35 years of age.
a. At the time of the 14 June 2023 data cutoff date, 31 adults had achieved platelet engraftment and were included in the analysis. One patient achieved platelet engraftment on Study Day 26, two days after the 14 June 2023 data cutoff date.

Figure 22: Median Neutrophil (top) and Platelet (bottom) Counts over Time in Adolescent and Adult Participants, through 2 Years of Follow-up (Study 121, FAS)



BL=baseline; FAS= Full Analysis Set; N=total sample size; SAS=Safety Analysis Set.
Note: Error bars represent the 1st and 3rd quartiles around the median.
* Common Terminology Criteria for Adverse Events (CTCAE): for neutrophil count = 1.5 × 10^9/L to < lower limit of normal; for platelet count = 75 × 10^9/L to < lower limit of normal.

8.5.2 Safety by Sex, Race, Genotype, and Geographic Region

The safety profile of exa-cel was consistent across additional subgroups, with AEs (including Grade ≥ 3 AEs and SAEs) being mostly aligned with the use of busulfan for myeloablative conditioning, HSCT, underlying disease, or medical history. No clinically relevant differences attributable to exa-cel were identified based on gender, race, genotype, or geographic region.

8.6 Potential Infusion-Related Reactions

No clinically significant infusion-related reactions were observed, and the exa-cel infusion was well tolerated.

After exa-cel infusion, 6 (13.6%) patients had potential infusion-related AEs, all of which are known side effects of busulfan[84], which patients received less than 1 week before exa-cel infusion. The only potential infusion-related reaction to occur in > 1 patient was abdominal pain (3/44 [6.8%]), and all potential infusion-related AEs were mild or moderate in severity. No patient had a Grade ≥ 3 or serious potential infusion-related AE, and there were no anaphylactic reactions at any time.

8.7 HSCT-Associated Complications

HSCT-associated complications are well-recognized clinical findings that can include transplant-related mortality, graft failure, graft rejection, and acute or chronic GVHD. Other peri-transplant complications include febrile neutropenia, infections, bleeding, and veno-occlusive liver disease.[53, 117-119]

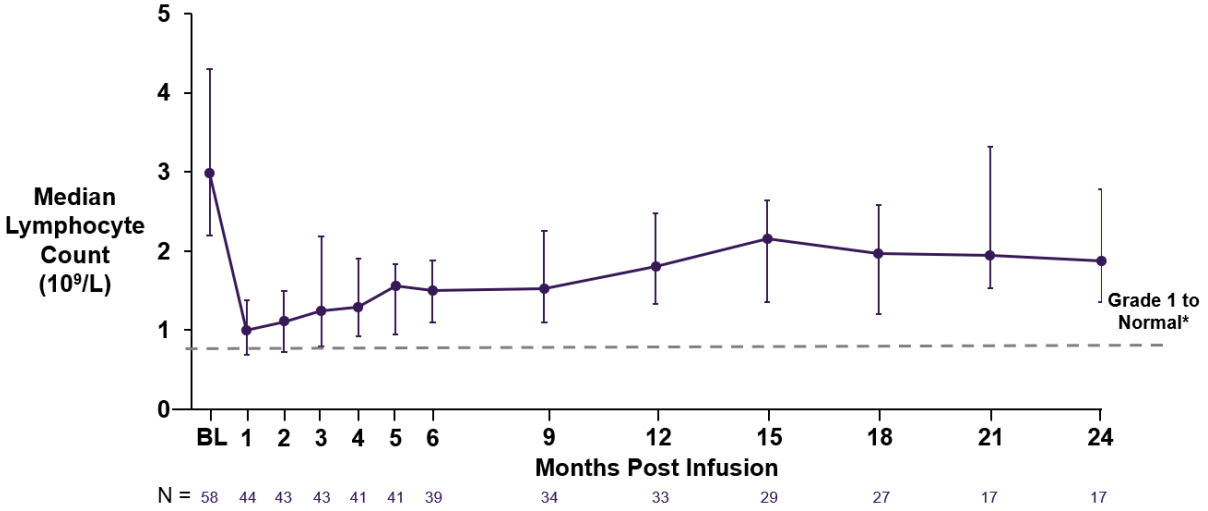
Analysis of HSCT-associated complications revealed no concerns specific to exa-cel. Overall, the pattern, incidence, and severity of AEs reported during the peri- and post-transplant periods were consistent with myeloablative conditioning and autologous HSCT. No patient had graft failure (primary or secondary), and none had graft rejection or GVHD, neither of which were anticipated given exa-cel's autologous nature.

8.8 Laboratory Values

Lymphocytes

Consistent with autologous HSCT, median lymphocyte counts were lowest at Month 1 and increased thereafter (Figure 23). After exa-cel infusion, median lymphocyte values were 1.0×10^9/L at Month 1 and then increased steadily through Month 5, after which time the median values remained ≥ 1.5×10^9/L.

Figure 23: Median Lymphocyte Counts over Time (Study 121, SAS)



BL=Baseline; N=total sample size; SAS=Safety Analysis Set.
Notes: Analysis was performed on the Safety Analysis Set (N=58), which includes all patients who started the mobilization regimen. Mobilization started with subcutaneous plerixafor 2-to-3 hours before the start of apheresis to collect peripheral blood mononuclear cells (PBMCs). Median values are plotted in the line, and first and third quartile values are plotted as bars at each visit. The numbers of patients with values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement collected before the start of mobilization. Error bars represent the 1st and 3rd quartiles around the median.
* Common Terminology Criteria for Adverse Events (CTCAE): 0.8 × 10^9/L to < lower limit of normal.

Other Laboratory Values — Erythropoietin

After exa-cel infusion, there were no clinically relevant changes from baseline in erythropoietin levels. Individual erythropoietin levels generally remained stable and did not increase over time across all HbF levels observed. No evident change in erythropoietin levels was observed when HbF levels represented ~40% of total hemoglobin

8.9 Long-Term Safety: Study 131 Results

Study 131 continues the evaluation of safety and efficacy after exa-cel in SCD and TDT patients who completed or discontinued pivotal Studies 121 (SCD) and 111 (TDT) for a total of 15 years following exa-cel infusion. The primary objective of the study is the long-term safety of exa-cel. The primary endpoints, include:

- New malignancies
- New or worsening hematologic disorders (e.g., immune-mediated cytopenias, aplastic anemia, primary immunodeficiencies)
- All-cause mortality
- All SAEs
- CTX001-related AEs and SAEs

As of the June 2023 data cutoff date, a total of 17 patients with SCD had enrolled in Study 131 after completing the Month 24 Visit in Study 121 (Table 36). The overall duration of follow-up (including follow-up in Study 131) for these 17 patients ranged from 25.1 to 48.1 months after exa-cel infusion. AE collection included: nonserious AEs considered related or possibly related to exa-cel, all SAEs regardless of relatedness, and all complications from SCD, new malignancies, and new or worsening hematologic disorders, regardless of relatedness or seriousness.

Overall, no new safety findings were observed for patients enrolled in the long-term follow-up Study 131, including no evidence of new malignancies or new or worsening hematologic disorders. No patient had an AE related to SCD while in long-term follow-up.

No deaths have occurred during Study 131, and no AEs of new malignancies or new or worsening hematologic AEs have occurred at any time after exa-cel infusion. One patient had an SAE of gastroenteritis norovirus on Study Day 799 (approximately 2.2 years after exa-cel infusion). The event was considered unrelated to any study drug and resolved within 4 days.

Neutrophil, platelet, and lymphocyte count values were maintained through Study 131, with median values increasing or remaining stable over time.

Table 36: Summary of Long-term Safety (Study 131)

Parameter:	Study 131
Patients enrolled in Study 131	17
Maximum duration of follow-up, months	48.1
Patients with AEs > 24 months after exa-cel infusion	
AEs considered as related or possibly related to exa-cel	0
SAEs	1 (5.9)[a]
New malignancies	0
Patients who discontinued Study 131 due to an AE	0

AE=adverse event; SAE=serious adverse event.
a. One patient had an SAE of gastroenteritis norovirus on Study Day 799 (approximately 2.2 years after exa-cel infusion). The event was considered unrelated to any study drug and resolved within 4 days.

8.10 Risk of Hematologic Malignancy

As of the 14 June 2023 data cutoff date, which includes up to 4 years of follow-up, there have been no cases of hematologic malignancy in the exa-cel program. While there is a known risk of hematologic malignancy with busulfan and HSCT, particularly in the setting of non-myeloablative conditioning or graft failure in allo-HSCT, there has been no evidence from extensive non-clinical investigations or clinical experience of any additional malignancy risk from exa-cel treatment.

The absolute risk of patients with SCD developing acute myeloid leukemia (AML) is low. In an observational study of 6,423 patients followed for a median of 22.2 person-years, 6 of 6,423 patients developed AML, for an absolute risk of 0.1%.[120]

There is a known risk of hematologic malignancy after allogeneic HSCT in patients with HSCT. In a study with both myeloablative and non-myeloablative busulfan-based regimens, the overall 10-year incidence of hematological malignancy was 1.7%.[21] The incidence appears to be lower in the setting of full myeloablative conditioning; a retrospective study of 234 patients with SCD in France with a median of 7.9 years of follow-up after allogeneic-HSCT found that none had developed AML.[56] The incidence of hematologic malignancies appears higher (~4%) in patients with SCD following both non-myeloablative allogeneic-HSCT[21, 121] and HSCT with lentivirus-based gene therapy.[73, 122] Specifically, factors that increase risk of hematologic malignancy include the use of non-myeloablative conditioning and graft failure or rejection.[21] The elevated risk of hematological malignancy following non-myeloablative conditioning may be due to the exposure of endogenous cells to the genotoxic conditioning regimen at doses insufficient to eliminate those cells potential for future growth as well as graft failure or rejection.[21]

None of these additional risk factors apply with exa-cel, which utilizes full myeloablative conditioning with busulfan and, as a non-viral approach, carries no risk of insertional mutagenesis.

Nonetheless, surveillance for hematologic malignancies is a key safety activity, and the Sponsor will continue to monitor patients as part of its pharmacovigilance activities post-approval (Section 8.11), including two 15-year follow-up studies, Study 131 and a post-approval, registry-based, prospective observational study.

In conclusion, while there is a known risk of hematologic malignancy with busulfan and HSCT, particularly in the setting of non-myeloablative conditioning or graft failure in allo-HSCT, there is no evidence from extensive non-clinical investigations or clinical experience of any additional risk from exa-cel treatment. Nonetheless, long-term surveillance will continue through the ongoing Study 131 and the proposed post-approval 15 year registry-based study.

8.11 Pharmacovigilance Plan

The sponsor proposes the following activities as part of their pharmacovigilance (PV) plan:

1. Product labeling describing exa-cel must be used in conjunction with busulfan myeloablative conditioning and HSCT and reference to the attendant risks associated with the myeloablative conditioning agent (busulfan), as well as the exa-cel specific risk of delayed platelet engraftment
2. Continuation of the long term extension Study 131
3. Establishment of a long-term registry-based study to follow patients treated with commercial exa-cel product post approval

The totality of safety data demonstrates that exa-cel is safe and well tolerated in both adolescents and adults and supports a favorable benefit-risk in both populations. The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk.

Exa-cel will be administered in a treatment center by a physician with experience in HSCT and in the treatment of patients with β-hemoglobinopathies. Safety manifestations of myeloablation followed by exa-cel infusion are both monitorable and manageable by physicians and treatment

centers with experience in HSCT. The proposed product information includes guidance and relevant information from the clinical trial experience, including AEs, SAEs, and engraftment.

The long-term safety of exa-cel will be further characterized in the ongoing Study 131, where patients who received exa-cel will be followed for 15 years after treatment. Additionally, the Sponsor proposes patients treated with commercial exa-cel drug product post-approval will be followed for 15 years through a post-approval, registry-based, prospective study.

The objectives of the 15-year registry-based study are to evaluate relevant safety and efficacy endpoints in patients with SCD treated with exa-cel in the real-world setting post-approval. Leveraging established transplant Registries in the US and EU, key endpoints include:

Safety: Neutrophil and platelet engraftment/recovery; New malignancies; Hematologic disorders; Mortality/survival

Effectiveness: Severe VOCs; Hb/HbF/HbS; Disease-related end organ damage

Post-marketing surveillance will be performed with the use of standard pharmacovigilance activities, including active follow-up of relevant clinical events e.g., delayed neutrophil or platelet engraftment, and any hematologic malignancy.

In conclusion, the safety profile of exa-cel is consistent with that of myeloablative busulfan conditioning and HSCT. In combination with robust post-approval pharmacovigilance surveillance, including the ongoing long-term Study 131 and the proposed 15-year post-approval registry-based study to follow patients treated with commercial product, the product labeling (USPI and patient information) is considered appropriate to communicate the relevant safety information for use of exa-cel.

8.12 Safety Conclusions in Sickle Cell Disease

The safety of exa-cel has been comprehensively evaluated in non-clinical and clinical studies, both of which demonstrated a favorable safety profile.

Extensive off-target assessment in $CD34^+$ samples from both healthy donors and SCD patients revealed no detectable off-target edits or evidence of chromosomal abnormalities following treatment with exa-cel.

The clinical safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment being the only exa-cel specific risk.

No patients experienced an SAE which was related or possibly related to exa-cel. The safety of exa-cel was also consistent across adult and adolescent sub-groups.

The most common AEs were nausea (70.5%), stomatitis (63.6%), vomiting (56.8%) and febrile neutropenia (54.5%), all of which are common manifestations following busulfan administration and HSCT.

Most AEs, SAEs and Grade 3 or higher AEs occurred within the first 3-6 months after myeloablation and exa-cel administration and decreased thereafter.

Following infusion with exa-cel, all patients (N=44) achieved neutrophil engraftment by Study Day 43. No patient had neutrophil engraftment failure, and none received backup $CD34^+$ cells. Likewise, all patients have also achieved platelet engraftment.

No safety findings related to exa-cel have been noted in patients in long-term follow-up, including no hematologic malignancies.

In conclusion, the safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk. The safety data for exa-cel supports a favorable benefit-risk in adults and adolescents with SCD.

9 BENEFIT-RISK CONCLUSIONS

Exagamglogene autotemcel (exa-cel) is a one-time, single dose cellular product consisting of autologous CD34+ human hematopoietic stem and progenitor cells (hHSPCs) modified by CRISPR/Cas9-mediated gene editing that was developed to treat patients 12 years and older with severe sickle cell disease (SCD).

SCD is a serious, rare, debilitating, and life-shortening hemoglobinopathy with no broadly available curative options. SCD affects approximately 100,000 people in the US. Patients with severe SCD, as defined by recurrent vaso-occlusive crises (VOCs), are even more rare, estimated at 20,000 people in the US. In the US, approximately 90% of people with SCD are of African descent.[1] This demographic distribution contributes to SCD patients historically facing significant healthcare disparities which directly relate to the poor outcomes associated with SCD.[1] Overall SCD patient lifespan is shortened by 2 to 3 decades compared to the general population. The median age at death is 45 years[5], with some patients only surviving to 20 years.[4] Patients with severe disease have even greater morbidity and mortality, including increased mortality in adults and adolescents.[2-4, 7, 9, 52]

The exa-cel development program in SCD consists of Study 121, a pivotal Phase 1/2/3 study, and Study 131, a long-term safety and efficacy follow-up study. The pivotal study included pre-specified interim analyses, and as described in this briefing document, the Sponsor proposes the data from these analyses can support either traditional or accelerated approval by the FDA.

The primary efficacy endpoint in Study 121 was absence of severe VOCs for at least 12 consecutive months (VF12) to support a traditional approval. The study also included evaluation of a surrogate efficacy biomarker, HbF (%) ≥ 20% at Month 6, and an interim clinical endpoint (ICE), absence of severe VOCs for at least 9 consecutive months (VF9), to support accelerated approval. The efficacy of exa-cel is transformational and consistent across subgroups of age (≥12 to <18 and ≥18 to 35 years), sex, baseline VOC, and disease genotype. Overall:

- 29 of 30 (96.7%) patients in the PES achieved VF12, including 6 adolescent patients
- 30 of 30 (100%) patients in the PES achieved HF12, including 6 adolescent patients

Results for the surrogate efficacy biomarker, HbF% ≥20% at 6 months and the intermediate clinical endpoint (ICE), VF9 in the EES, are equally robust:

- 40 of 40 (100%) patients achieve the surrogate efficacy biomarker of HbF ≥ 20% at Month 6, including 11 adolescent patients
- 31 of 32 (97%) patients achieve the intermediate clinical endpoint (ICE), VF9, including 7 adolescent patients

The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and HSCT, with delayed platelet engraftment the only exa-cel specific risk. There were no clinically significant differences in observed AE profile between adult and adolescent subjects (the same was observed for sex, race, and genotype).

Post approval, to ensure safe use of exa-cel, the Sponsor considers product labeling (USPI and patient information) to communicate the relevant safety information for use of exa-cel and post-

marketing pharmacovigilance (PV) surveillance to be sufficient and appropriate. In addition to standard post marketing PV surveillance, the Sponsor's PV program also includes follow-up of subjects enrolled and dosed in Study 121 for 15 years in the long term follow-up study (Study 131), as well as a proposed post-approval 15-year registry-based study to follow patients treated with commercial product.

Taken together, the results from the exa-cel program in severe SCD are unprecedented. Exa-cel has demonstrated transformative efficacy, a strong safety profile, and a highly positive benefit-risk profile for treatment of severe sickle cell disease patients.

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11 APPENDICES

11.1 Full Inclusion/Exclusion Criteria for Studies 121 and 131

11.1.1 Study 121 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Patient (or their legally authorized representative or guardian) signed and dated an informed consent form (ICF) and, where applicable, an assent form.
2. Patients 12 to 35 years of age, inclusive, on the date of informed consent.
3. Documented β^S/β^S, β^S/β^0, or β^S/β^+. Patients could enroll based on historical genotype results, but confirmation of genotype was required before busulfan conditioning. The β^0 genotypes were defined using the HbVar Database.
4. Patients with severe SCD. Severe SCD was defined by the occurrence of at least 2 of the following events per year during the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan, HU):

    - Acute pain event that required a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions
    - ACS, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
    - Priapism lasting > 2 hours and requiring a visit to a medical facility
    - Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in Hb concentration of ≥ 2 g/dL.
    - Historical severe VOCs were adjudicated by the Endpoint Adjudication Committee (EAC).

5. Normal transcranial Doppler (TCD) velocity (time-averaged mean of the maximum velocity [TAMMV] < 170 cm/sec for non-imaging TCD and < 155 cm/sec for imaging TCD) in the middle cerebral artery (MCA) and the internal carotid artery (ICA) for patients 12 to 16 years of age
6. Karnofsky performance status of ≥ 80% for patients ≥ 16 years of age or Lansky performance status of ≥ 80% for patients < 16 years of age.
7. Eligible for autologous stem cell transplant as per investigator's judgment.
8. Female patients of childbearing potential (postmenarcheal, had an intact uterus and at least 1 ovary, and was less than 1 year postmenopausal) agreed to use acceptable method(s) of contraception from consent through at least 6 months after exa-cel infusion.
9. Male patients of reproductive capacity agreed to use effective contraception from start of mobilization through at least 6 months after exa-cel infusion.
10. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, contraceptive guidelines, and other study procedures.
11. Willing to participate in the long-term follow-up study (Study 131), after completion of this study.

Exclusion Criteria

1. An available 10/10 human leukocyte antigen (HLA)-matched related donor.
2. Prior HSCT.
3. Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator.
4. White blood cell (WBC) count < 3×10^9/L or platelet count < 50×10^9/L, not related to hypersplenism per investigator judgment.
5. Treatment with regular RBC transfusions that, in the opinion of the investigator, could not be interrupted after engraftment.
6. Patients with history of alloimmunization to RBC antigens and for whom the investigator anticipates that there would be insufficient RBC units available for the duration of the study.
7. More than 10 unplanned hospitalizations or emergency department visits related to SCD in the 1 year before screening that, in the opinion of the investigator, were consistent with significant chronic pain rather than acute pain crises.
8. HbF level > 15.0%, irrespective of concomitant treatment with HbF-inducing treatments such as HU.
9. History of abnormal TCD (TAMMV ≥ 200 cm/sec for non-imaging TCD and ≥ 185 cm/sec for imaging TCD) for patients 12 to 18 years of age.
10. History of untreated Moyamoya disease or presence of Moyamoya disease at Screening that in the opinion of the investigator put the patient at the risk of bleeding.
11. History of a significant bleeding disorder.
12. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the patient. This could include, but was not limited to: history of relevant drug allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; history of mental disease; or history of familial cancer syndrome.
13. Any prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder.
14. Advanced liver disease, defined as:
    a. Alanine transaminase (ALT) > 3 × the upper limit of normal (ULN) or direct bilirubin value > 2.5 × ULN or
    b. Baseline prothrombin time (international normalized ratio [INR]) > 1.5 × ULN, or
    c. History of cirrhosis or any evidence of bridging fibrosis, or active hepatitis on liver biopsy.
15. Baseline estimated glomerular filtration rate < 60 mL/min/1.73 m2.
16. Lung diffusing capacity for carbon monoxide (Dlco) < 50% of predicted value (corrected for Hb and/or alveolar volume).
17. Left ventricular ejection fraction (LVEF) < 45% by echocardiogram.
18. Prior treatment with gene therapy/editing product.
19. Intolerance, contraindication, or known sensitivity to plerixafor or busulfan. Patient had no risk factors in the opinion of the investigator that would have increased the likelihood of busulfan-related toxicities. Prior anaphylactic reaction with excipients of exa-cel product (dimethylsulfoxide [DMSO], dextran).
20. Positive for the presence of human immunodeficiency virus-1 (HIV-1) or human immunodeficiency virus-2 (HIV-2) (positive for both antigen/antibody AND nucleic acid

tests [NAT]), hepatitis B virus (HBV) (positive for Hepatitis B core antibody [HbcAb] or positive hepatitis B surface antigen [HbsAg] AND NAT tests), syphilis (positive screening AND positive confirmatory tests), or hepatitis C virus (HCV; positive for both antibody [HCAb] AND for NAT tests). Additional infectious disease markers were obtained and tested as required by the local authority for the collection and processing of cellular therapy products. These additional tests (e.g., human T-cell lymphotropic virus-1 [HTLV-1], human T cell lymphotropic virus-2 [HTLV-2], malaria, tuberculosis, toxoplasmosis, Trypanosoma cruzi, or West Nile virus) were evaluated to determine overall impact to the patient and manufacturing of exa-cel.

21. Participation in another clinical study with an investigational drug/product within 30 days of screening or fewer than 5 half-lives of the investigational agent, whichever was longer from screening.
22. Patients who were not able to comply with the study procedures outlined in the protocol as judged by the investigator.
23. Pregnancy or breastfeeding.

11.1.2 Study 131 Inclusion/Exclusion Criteria

Inclusion Criteria

Patients who met all of the following inclusion criteria were eligible for enrollment:

1. Patients (or his or her legally appointed and authorized representative or guardian) signed and dated ICF and, where applicable, an assent form.
2. Patients received exa-cel infusion in a parent study.

Exclusion Criteria

There were no exclusion criteria.

11.2 Supplemental Safety Information

11.2.1 Patient SAE Vignettes

No patient in Study 121 had an SAE considered related or possibly related to exa-cel (Section 8.2.5).

Death in Study 121: The adult patient (33 years of age) with SCD had 3.0 severe VOCs per year in the previous 2 years before enrollment in Study 121 and had pre-existing lung disease. After exa-cel, the patient had an uneventful course with neutrophil and platelet engraftment achieved at times consistent with other patients in the study. The patient had an AE of COVID-19 on Day 71 in an out-patient setting and was subsequently hospitalized for an extended duration (Days 112 to 268). During this time, the patient had SAEs of pneumonia, hypoxia and respiratory failure which were diagnosed to be due to COVID-19, with a potential contribution of busulfan lung injury and pre-existing lung disease. The patient had a protracted course in the intensive care unit with intubation and extracorporeal membrane oxygenation support. The SAEs were determined by the investigator as unrelated to exa-cel and related to COVID-19 and busulfan. Lung injury and serious infections, including fatal outcomes, are known risks of busulfan treatment.[84]

11.2.2 Reference Ranges for Neutrophil and Platelet Engraftment

Table 37: Reference Ranges for Neutrophil and Platelet Engraftment for Allo- and Auto-HSCT

Median (range) Time to Engraftment, days:	Neutrophils	Platelets
Exa-cel SCD	27 (15, 40)	35 (23, 126)
Other Auto-HSCT Gene Therapy in SCT		
Lovo-cel (Kanter) (N=35)	20 (12, 35)	36 (18, 136)
Allo-HSCT in SCD		
Dedeken (N=50)	19 (7, 53)	28 (9, 232)
Shah (N=62)[a]	13 (10, 34)	19 (12, 71)

Allo=allogenic; auto=autologous; HSCT=hematopoietic stem cell therapy; SCD=sickle cell disease.

a. All patients received granulocyte colony-stimulating factor starting at Day 7 until absolute neutrophil count was > 1.5 × 103 cells/mL for 3 days.

Sources: References[73, 113, 116]