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Division / Office	BHB/DCEH/OTP
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Priority Review	Yes
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Review Completion Date / Stamped Date	December 08, 2023 Revised April 09, 2024
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Applicant	Vertex Pharmaceuticals Inc
Established Name	Exagamglogene autotemcel
(Proposed) Trade Name	CASGEVY
Pharmacologic Class	Autologous CD34+ Hematopoietic Stem and Progenitor Cells edited ex vivo with CRISPR-Cas9
Dosage Form(s) and Route(s) of Administration	Exagamglogene autotemcel is a cell suspension for intravenous infusion at a single cell dose of $\geq 3.0 \times 10^6$ CD34+ cells/kg
Dosing Regimen	One-time treatment
Indication(s) and Intended Population(s)	Treatment of patients 12 years and older with sickle cell disease with recurrent vaso occlusive crises

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GLOSSARY

AA	accelerated approval
ACS	acute chest syndrome
BCL11A	B-cell lymphoma/leukemia 11A
BLA	Biologics License Application
Cas9	CRISPR-associated 9 nuclease
CD	Cluster of differentiation
CI	confidence interval
COVID-19	coronavirus disease 2019
CRISPR	Clustered regularly interspaced short palindromic repeats
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats and CRISPR-associated 9 nuclease
CSR	clinical study report
DCOD	Data cutoff date
DNA	Deoxyribonucleic acid
EAC	endpoint adjudication committee
eCTD	electronic common technical document
exa-cel	exagamglogene autotemcel, formerly CTX001
FAS	Full Analysis Set
F-cell	circulating red blood cells expressing detectable levels of HbF
FDA	Food and Drug Administration
F/U	follow up
G-CSF	granulocyte colony-stimulating factor
Hb	hemoglobin
HbA	adult hemoglobin
HbF	fetal hemoglobin or γ -globin
HbS	sickle hemoglobin
hHSPCs	human hematopoietic stem and progenitor cells
HLA	human leukocyte antigen
HPFH	hereditary persistence of fetal hemoglobin

HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
IA	interim analysis(es)
IA1	interim analysis 1
IA2	interim analysis 2
IA3	interim analysis 3
ICE	intermediate clinical endpoint
IND	Investigational New Drug (application) (US)
IV iv	intravenous, intravenously
max	maximum
min	minimum
MOA	mechanism of action
PES	Primary Efficacy Set
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCA	sickle cell anemia
SCD	sickle cell disease
SD	standard deviation
SE	standard error
sVOC	severe vaso-occlusive crisis as defined in Study 121
TAMMV	time-averaged mean of the maximum velocity
TCD	transcranial Doppler
TDT	transfusion-dependent thalassemia
VF9	Intermediate clinical efficacy endpoint in Study 121. Absence of any severe vaso-occlusive crisis for at least 9 consecutive months within the 24-month follow up period in Study 121. See text for full definition.
VF12	Primary efficacy endpoint in Study 121. Absence of any severe vaso-occlusive crisis for at least 12 consecutive months within the 24-month follow up period in Study 121. See text for full definition.

VOC	vaso-occlusive crisis
WRO	Written Response Only

1. Executive Summary

Exa-cel is a one-time, single-dose, autologous cellular product modified by *ex vivo* CRISPR/Cas9-mediated gene editing of the BCL11A gene to increase fetal hemoglobin (HbF) expression for prevention of severe vaso-occlusive crisis (sVOC) in severe sickle cell disease (SCD).

Data package and study design

The clinical development program of exa-cel for SCD consists of Study 121, the main 24-month study, and Study 131, the long-term follow-up (LTFU) study, for a total follow-up (F/U) of up to 15 years after exa-cel infusion.

Study 121 was a single-arm, multi-site trial in subjects with severe SCD, aged 12 to 35 years, inclusive. Eligibility criteria include documented genotypes of $\beta S/\beta S$, $\beta S/\beta 0$, or $\beta S/\beta +$. Subjects were required to have at least two protocol-defined severe VOCs (sVOCs) during each of the two years prior to enrollment (i.e., baseline period). The protocol-defined sVOCs include acute pain, acute chest syndrome, priapism, and splenic sequestration. An Endpoint Adjudication Committee (EAC) were to adjudicate all sVOCs reported by the investigators, both for the retrospective baseline period and for the period after exa-cel infusion. Subjects with significant chronic pain rather than acute pain crises were excluded.

In Study 121, subjects were to undergo mobilization and apheresis collection of CD34+ cells for manufacture of autologous exa-cel, followed by myeloablative conditioning and infusion of exa-cel. Subjects were then to receive RBC transfusions for post-transplant support or SCD management and be followed up for 24 months after exa-cel infusion to be assessed for efficacy and safety endpoints. The follow-up (F/U) schedule was monthly for the first 6 months, and then every 3 months thereafter until Month 24. All subjects who receive exa-cel will be asked to enroll in the LTFU study, Study 131, after completion or withdrawal/discontinuation from Study 121, for a total F/U of up to 15 years after exa-cel infusion. The F/U schedule in Study 131 is every 3 months until the end of Year 3 after exa-cel infusion, every 6 months for Year 4 and Year 5, and annually thereafter.

The primary efficacy endpoint was the proportion of VF12 responders, i.e., patients who have not experienced any sVOC for at least 12 consecutive months after exa-cel infusion during the 24-month F/U in Study 121. Evaluation period for VF12 response starts 60 days after the last RBC transfusion for post-transplant support or SCD management. The planned primary efficacy analysis was the observed VF12 response rate compared to a 50% null response rate.

The planned sample size was 45 subjects with three interim analyses (IAs).

Of the 63 subjects screened in Study 121, a total of 58 SCD subjects started stem cell mobilization and formed the safety database. Of these, a total of 44 subjects received exa-cel and formed the Full Analysis Set (FAS). The Primary Efficacy Set (PES) consists of a subset of 30 FAS subjects who had at least 16 months of F/U after exa-cel infusion. The FAS formed the efficacy database, with PES as the primary analysis set for main efficacy outcomes.

The data package reviewed in this memo was based on the 3rd IA with an allotted one-sided type 1 error rate of 0.02 for analyses based on PES.

There are several issues with the definition of the VF12 response. It is different from a more natural definition for user interpretation where efficacy evaluation would start from the time when the therapy starts taking effect, e.g., Months 7 to 18, inclusive, after investigational product administration. There are multiple types of flexibility in the definition of the protocol-defined VF12 response, e.g., the 12-month sVOC-free period can be achieved anywhere within the 24-month F/U period. This flexibility in the evaluation period alone would lead to at least a 2-3 folds increase in the chance of observing a response when there is no treatment effect, compared to a fixed-period (e.g., Months 7 to 18) response endpoint. I find the Applicant's rationales for the choice of a 50% VF12 null response rate inadequate by failing to address the flexibilities in the VF12 response definition, even though they acknowledged that these would affect the null. Therefore, I do not recommend reporting study results on VF12 in terms of a p-value testing the VF12 response rate against a null rate of 50%.

Efficacy results

In the PES (N=30), at baseline 77% of the subjects had ≤ 4.5 sVOCs/year, with a range of 2.0 to 9.5 sVOCs/year. There are roughly equal numbers of males and females. The primary analysis of the primary efficacy endpoint, VF12 response rate, was a point estimate of 93.5% (29/31) with a one-sided 98% confidence interval (CI) of (77.9%, 100%). The Applicant proposed to include only those subjects with at least 16 months of F/U after exa-cel infusion in PES. However, an additional non-PES subject, with 14.3 months of F/U and three sVOCs at Months 11.7, 12.8, and 14.1, was clearly a VF12 non-responder and is therefore included in the estimate of the VF12 response rate.

A death occurred on Day 268 (Month 8.9). I proposed to include this death as a VF12 non-responder, as it was reported by the investigator to be related to COVID-19 and busulfan, the latter being an integral component of the exa-cel treatment regimen. I ultimately agreed with the FDA clinical team's decision to exclude this subject from the efficacy analysis as it is challenging to delineate the role of busulfan in the death among the multiple comorbidities.

Of the two VF12 non-responders, Subject (b) (6) experienced 9 acute pain episodes with emergency room visits from Day 364 to Day 821 (Months 12.1 to 27.4), and Subject

(b) (6) experienced 3 acute pain episodes with emergency room visits from Day 350 to Day 424 (Month 11.7 to 14.1). A VF12 responder, Subject (b) (6), experienced an acute pain episode that required a 5-day hospitalization starting Day 639 (Month 30.0) after initially achieving VF12 response.

Of the remaining 12 subjects whose VF12 response status could not yet be determined at IA3 and therefore were not included in the primary efficacy analysis, 3 subjects experienced acute pain episodes determined to meet the sVOC definition. In two of these subjects, the sVOCs were associated with hospitalizations: one subject had 1 sVOCs at Month 9.9 and the other had 2 sVOCs at Months 2.3 and 6.2, respectively. The third subject had an acute pain episode with an outpatient clinic visit on Month 4.2.

Several issues complicate the interpretation of the magnitude of and the assessment of the robustness of exa-cel's treatment effect in terms of VF12 response rate, the primary efficacy endpoint.

- Contrary to a more natural response definition with response evaluation starting at a fixed time point when exa-cel were expected to take effect, e.g., Month 7, Study 121 defined VF12 response status with multiple types of flexibilities, some of which were introduced while study data had become available. One such flexibility was that any 12-month sVOC-free period during the 24-month F/U period would qualify as a VF12 response. This flexibility alone would increase the null response rate to at least 2-3 folds of the null response rate for a fixed-period response definition. The 50% response rate chosen by the Applicant therefore was not well supported by the Applicant's rationales, which did not consider the effect of any of the flexibilities. The unique VF12 response definition in Study 121 makes it difficult to identify a null response rate against which to compare the exa-cel response rate.
- VF12 response determination included only sVOCs adjudicated by the EAC, and only potential sVOCs reported by the investigator received EAC adjudication. In addition, there appears to be a lack of a standardized and structured approach to ensure all VOCs were recorded by the study subjects and were reported to the investigators. Whether this process introduced biases, and the extent of biases in the single-arm study, are unknown.
- There appears to be potential over-counting of baseline sVOCs, indicated by the observation that 8 of the 21 subjects reported to have ≤ 3 sVOCs/year during baseline had at least two sVOCs separated by 20 days or less.
- One clinical site contributed around 50% of efficacy data for the IA, with an indication of better results at this site compared to other sites on average.
- The limited sample size (N=31) and F/U at the IA limited assessment of the robustness of the treatment effect across subgroups defined by various factors. For

example, only 7 adolescents were evaluable for VF12 response, and only one subject had the β^S/β^0 genotype.

- The Applicant revised the protocol and the statistical analysis plan (SAP) substantially while Study 121 was ongoing, with the final SAP containing some revisions submitted only at the time of the BLA submission. The FDA review team did not agree with all of these revisions.

Despite the limitations of the efficacy results, I conclude that the overall study result indicates that exa-cel is effective during the F/U. This conclusion is based in part on consultation with the clinical review team, and supported by the clear mechanism of action and the stable expression of HbF during the F/U period.

Safety results

One death occurred in Study 121, to a 33-year-old Black female participant on Day 268 (Month 8.9). The investigator determined that the death was not related to exa-cel, but rather was related to COVID-19 and busulfan. However, busulfan is an integral component of the exa-cel treatment regimen.

The Applicant concluded that *“The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and [hematopoietic stem cell transplantation] HSCT, with delayed platelet engraftment the only exa-cel specific risk identified.”* It should be noted that at this time busulfan conditioning is an integral component of the exa-cel treatment regimen. Therefore, when assessing the benefit-risk profile of exa-cel, the risk associated with the entire treatment regimen, including busulfan conditioning, should be considered.

The issue of on-target and off-target unintended genetic modification was investigated by the Applicant and discussed at an advisory committee meeting. It appears impracticable to draw any conclusion in pre-marketing studies. The Applicant plans to investigate this issue further through the 15-year LTFU study (Study 131) for patients who received exa-cel in their clinical trials and a 15-year registry-based prospective observational study for patients who will receive commercial exa-cel. Please refer to review memos by other relevant review disciplines for more information.

Conclusions and recommendations

Exa-cel is effective for prevention of protocol-defined severe vaso-occlusive crises in patient with severe sickle cell diseases. The limited sample size and follow-up duration of the interim analysis data package in this BLA limit assessment of the durability and the robustness of the treatment effect in the single-arm trial. We will be able to assess these aspects more fully when the final analysis data package becomes available, which will include at least 24 months of follow-up for all exa-cel treated subjects. I have recommended that the review committee send an information request to the Applicant, stressing the importance of timely reporting of the final study results once all treated

subjects in Study 121 have been followed up for 24 months, to enable a fuller assessment of the treatment effect.

2. Clinical and Regulatory Background

Original Biologics License Application (BLA) 125787/0 is a marketing application for exagamglogene autotemcel (exa-cel) for the proposed indication of treatment of sickle cell disease (SCD) in patients aged 12 years and older with recurrent vaso-occlusive crises (VOCs). An indication for treatment of transfusion-dependent thalassemia (TDT) in patients of the same age range is being sought under a separate BLA.

Exa-cel (CASGEVY), formerly known as CTX001, is a one-time, single-dose, autologous cellular product consisting of CD34+ human hematopoietic stem and progenitor cells (hHSPCs) modified *ex vivo* by CRISPR/Cas9-mediated gene editing of the intronic erythroid enhancer region of the BCL11A gene. It is intended to be a functional cure of SCD.

BCL11A codes for a transcriptional repressor of γ -globin and its expression leads to decreased fetal hemoglobin (HbF, $\alpha_2\gamma_2$) expression in adult tissues. The intended mechanism of action (MOA) of exa-cel is that the reduction of BCL11A gene transcription and the subsequent decrease in BCL11A protein level would lead to concomitant increases in γ -globin expression in SCD patients treated with exa-cel, which would lead to, upon erythroid differentiation, increased levels of HbF. The gene editing was intended to lower BCL11A transcription in erythroid cells only, while preserving the normal function of BCL11A in other cell types.

HbF is the dominant form of hemoglobin (Hb) present in the fetus during gestation. HbF is replaced by HbA ($\alpha_2\beta_2$), the adult form of Hb, by 6 to 12 months of age with typically less than 1% of HbF thereafter. In the general population, at birth there are 25% of HbA and 75% of HbF, while within the first year of life there are 95% of HbA, 2.5% of HbA₂ ($\alpha_2\delta_2$), and <1% of HbF. The switch from HbF to adult hemoglobin is mediated by a transcriptional switch from γ -globin to β -globin within the β -globin gene cluster located on chromosome 11.

Elevated levels of HbF are associated with improved morbidity and mortality in patients with SCD. Neonates and infants with SCD are typically asymptomatic while their HbF levels remain high and become symptomatic during the first year of life when the synthesis of HbF declines. It was observed that 10 patients with SCD who co-inherit hereditary persistence of fetal hemoglobin (HPFH), in which HbF production continues into adulthood, have little or no manifestation of SCD and are generally healthy. Individuals who have SCD and HPFH have 70% HbS in their RBCs but are neither anemic nor symptomatic. The uniform distribution of HbF among their RBCs interferes with HbS polymerization, increases its solubility, and prevents RBC sickling. Variants in multiple genes including BCL11A, a repressor of the HbF gene, have been found to increase HbF and reduce the severity of clinical consequences of SCD.

2.1 Disease or Health-Related Condition(s) Studied

Hemoglobinopathies are disorders caused by genetic defects that affect the production or function of hemoglobin molecules. Two of the most common of the hemoglobinopathies are sickle cell disease (SCD) and β -thalassemia. SCD is one of the most common monogenic disorders. It affects over 100,000 individuals in the United States (US) and about 42,000 individuals in Europe. In the US, approximately 90% of people with SCD are of African descent. Overall SCD patient lifespan is shortened by 2 to 3 decades compared to the general population; the median age at death is 45 years.

In SCD, a single point mutation within codon 6 of the β -globin gene causes glutamic acid to be replaced with valine and results in the production of an abnormal globin chain (β S-globin). High concentrations of hemoglobin (Hb) tetramers (composed of 2 β -globin and 2 α -globin subunits) that include β S-globin subunits (i.e., HbS) in red blood cells (RBCs) and subsequent polymerization under low oxygen conditions cause the RBCs to become sickled, sticky, and rigid, markedly reducing RBC lifespan, which manifests acutely as hemolytic anemia, vasculopathy, and vaso-occlusion. Repeated vaso-occlusive events (VOEs), progressive vasculopathy, and prolonged hemolytic anemia can result in chronic complications that lead to disease progression and end-organ damage, which are the primary causes of morbidity and mortality in adults with SCD. Despite the common genetic cause and pathophysiology of SCD, patients can experience complex, highly variable clinical manifestations of disease.

While SCD refers to all disease genotype, sickle cell anemia (SCA) refers to the homozygous HbSS genotype, the most common and most serious form of SCD, and the clinically similar genotype of HbS β 0-thalassemia.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Management of SCD is focused on preventing and treating pain episodes and other complications. Prevention and management strategies include:

- Lifestyle behaviors to help prevent and reduce the occurrence of pain crises, e.g., drinking plenty of water, avoiding getting too hot or too cold, avoiding high altitudes, and avoiding low oxygen levels
- Prevention of infections through lifestyle behaviors, vaccines, and antibiotics
- Monitoring and intervention to prevent vision loss, stroke, severe anemia
- Management of pain crises via intravenous fluids, pain-reducing medicine, and hospitalization for severe pain crises.

Currently, approved therapies to prevent complications of SCD include hydroxyurea (HU) and crizanlizumab in the US and EU, and L-glutamine oral powder and voxelotor in the US:

- Hydroxyurea (HU) is a well-tolerated oral antimetabolite drug, taken orally daily, approved “*to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises.*” It was initially approved in 1998 for adults and then in 2017 for pediatric patients 2 years of age and older. The mechanisms by which HU produces its beneficial effects in SCA patients are uncertain. Known pharmacologic effects of HU that may contribute to its beneficial effects include increasing HbF levels in RBCs, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium. Because of its overall safety profile and efficacy, guidelines from both the US and United Kingdom (UK) recommend HU as standard of care treatment for all individuals with HbSS and HbS/HbS β 0-thalassemia regardless of clinical severity as prevention/reduction of sickle-related complications.
- L-glutamine (ENDARI) is an amino acid, taken orally twice daily, approved in 2017 “*to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.*” Its MOA in treating SCD is not fully understood but is thought to work through improving oxidative stress phenomena involved in the pathophysiology of SCD.
- Crizanlizumab (ADAKVEO) is a selectin blocker, administered by intravenous (IV) infusion every 4 weeks, approved in 2019 “*to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with SCD.*” It slows or stops RBCs, white blood cells, and platelets from sticking to each other and to the inside of blood vessel walls.
- Voxelotor (OXBRYTA), taken orally daily, is “*a hemoglobin S polymerization inhibitor indicated for the treatment of SCD in adults and pediatric patients 4 years of age and older.*” It received accelerated approval (AA) in 2019 for patients aged 12 years and up, and AA in 2021 for patients aged 4 to 11 years. The AA was based on increase in Hb. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Red blood cell (RBC) Transfusions in SCD improve the oxygen-carrying capacity of blood and concomitantly dilute circulating sickled erythrocytes to improve microvascular circulation; they also suppress endogenous production of RBCs containing HbS. Simple RBC transfusion may be indicated for certain acute illnesses such as acute chest syndrome (ACS) or severe exacerbation of anemia with splenic or hepatic sequestration, or prior to elective surgery to reduce the high risk for postoperative sickle cell complications. Chronic transfusion is recommended for patients at high risk for stroke. More aggressive method, such as exchange transfusion, may be required for more severe acute complications, such as recurring episodes of ACS, multi-organ failure syndrome, or stroke. The most important potential complications of transfusions are alloimmunization to minor RBC antigens and iron overload.

Allogeneic hematopoietic stem cell transplant (HSCT) is currently the only potentially curative therapy for SCD. HSCT should be considered standard of care in individuals with SCD who have experienced a stroke or are at very high risk of stroke. Further, transplantation should be considered for all patients with neurologic injury, or frequent pain, or recurrent episodes of ACS, and who have a matched, related sibling donor. Ongoing studies are looking to optimize the transplant from alternative donors, such as birthing parents or siblings who are only half-matched. Transplantation is limited by the availability of suitable donors, estimated at 18%, and the various risks associated with it.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The 5th Development Safety Update Report, covering the period from March 05, 2022 through March 04, 2023, was submitted to Investigational New Drug application (IND) 18143 amendment 209 on May 03, 2023. The Applicant reported therein that initial marketing authorization applications for exa-cel were submitted during the reporting period to the European Union and Great Britain and remained under review.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1. Regulatory Activity

Date	Regulatory Activity
April 27, 2018	Original Submission of IND 18143, planned for development of both sickle cell disease (SCD) and transfusion-dependent beta-thalassemia (TDT) ^a
May 25, 2018	IND placed on clinical hold (CH)
October 10, 2018	IND CH removed
January 02, 2019	Exa-cel granted Fast Track Designation for treatment of SCD
May 05, 2020	Exa-cel granted Regenerative Medicine Advanced Therapy Designation for treatment of severe SCD and TDT
May 11, 2020	Exa-cel granted Orphan Drug Designation (ODD 19-7155) for treatment of SCD
August 9, 2022	<p>Pre-BLA meeting. FDA meeting minutes issued September 8, 2022.</p> <ul style="list-style-type: none"> FDA stated: “FDA acknowledged the sponsor’s proposal to submit to the BLA a data package that was larger than previous proposals, to consist of 30 exa-cel treated SCD subjects with a median duration of follow-up (F/U) of 24 months (range: 16 to 46 months), though FDA maintained our previous recommendation of at least 40 treated SCD subjects, each with at least 18 months of F/U.” The sponsor’s proposal to use intermediate clinical endpoint (ICE) with shorter F/U and biomarker HbF to support application for accelerated approval was also discussed.
November 3, 2022	BLA 125787/0/0 submitted, consisting of Part 1, the non-clinical component, of the planned 3-Part rolling submission
April 03, 2023	BLA 125787/0/8 and 125787/0/9 submitted, completing the rolling submission. These two submissions include Module 5, with clinical data cutoff date of February 10, 2023 at interim analysis (IA) 2, consisting of 20 exa-cel treated subjects, each with at least 16 months of follow-up, including 3 adolescents.
June 01, 2023	(b) (4), (b) (5)
June 02, 2023	(b) (4), (b) (5)
June 08, 2023	FDA filed the BLA, with the understanding that the Applicant will submit additional efficacy and safety data corresponding to IA3.

July 08, 2023	The Applicant submitted 90-Day Safety and Efficacy Update to the BLA (125787/0/36), with a new data cut-off date of June 14, 2023, corresponding to IA3 with 30 treated subjects, each with at least 16 months of follow-up, including 6 adolescents.
October 31, 2023	Advisory Committee meeting for exa-cel for the SCD indication

^a IND 18143 includes development information for both SCD and TDT, but this table lists only information related to SCD, unless TDT-related information occurred during the same regulatory activity.

Source: Reviewer's summary.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical development program of exa-cel in SCD includes the main study (Study 121) and one long-term follow-up (LTFU) study (Study 131). For the proposed indication of SCD in this BLA, the efficacy and safety database consists of data from Study 121 and those from the SCD patients in Study 131. See "Section 5.3 Table of Studies/Clinical Trials" for a summary of the studies.

Reviewer Comment #1: Not considering accelerated approval pathway

The Applicant requested consideration for both traditional approval and accelerated approval (AA) pathways based on an intermediate clinical endpoint (ICE) and the biomarker endpoint HbF at Month 6 post exa-cel treatment. The review committee decided to review the BLA for consideration of traditional approval only, as in this context considering AA will require evidence in more aspects than for considering traditional approval, e.g., on prediction performance of the ICE and HbF for the clinical efficacy endpoint.

End of Reviewer Comment #1.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical review includes documents in IND 18143, the original BLA 125787, information requests (IRs) from the FDA, and IR responses from the Applicant. When documents were available in both the IND and the BLA, I reviewed the IND

versions. Documents reviewed are listed below. Documents are BLA documents, unless explicitly noted otherwise.

- Protocols and Statistical Analysis Plans (SAPs) for Study 121 and 131 in both the BLA and the IND
- Meeting minutes under IND 18143
- Application Orientation Meeting (AOM) and Dataset Walkthrough Meeting slides, presented by the Applicant on May 9, 2023
- Module 1.14 Labeling, including IA3 updates
- Module 1.2 Reviewer's Guide
- Module 2.5 Clinical Overview, including the 90-day (IA3) addendum to the clinical overview submitted to amendment 36 of the original BLA
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 2.7.6 Synopses of Individual Studies
- Module 5.2 Tabular Listing of all Clinical Studies
- Module 5.3.5.2 Studies 121 and 131 Interim Clinical Study Reports (CSRs) and supporting documents and datasets, including IA3 updates
- Advisory Committee Meeting Briefing Document from the Applicant

5.3 Table of Studies/Clinical Trials

The clinical development program of exa-cel consists of six ongoing studies (Table 2), identified in this memo with the last three digits of the original study identifiers, e.g., Study VX18-CTX001-131 is referred to as Study 131 in this memo.

- Study 111 treated TDT subjects (aged 12 to 35 years, inclusive) and followed subjects for 2 years after exa-cel infusion.
- Study 121 treated subjects (aged 12 to 35 years, inclusive) with severe SCD and followed subjects for 2 years after exa-cel infusion.
- Study 131 is a LTFU study that will follow subjects who complete or discontinue from Studies 111, 121, 141, or 151 for a total of 15 years after exa-cel infusion.
- Study 141 will treat pediatric TDT subjects (aged 2 to 11 years, inclusive).
- Study 151 will treat pediatric subjects with severe SCD (aged 2 to 11 years, inclusive).

- Study 161 will treat 18 subjects with either TDT or severe SCD (aged 12 to 35, inclusive) and follow subjects for 1 year after exa-cel infusion, with the primary endpoint being HbF over time.
 - It appears that Study 161 is intended to explore various aspects of the treatment regimen. For example, the most recent version (Version 3.1, dated April 12, 2023) increased the sample size from 12 to 18 to support expanding the timing of plerixafor administration in SCD subjects from “2 to 3 hours” to “2 to 6 hours” before planned apheresis, to allow increased flexibility to optimize CD34+ cell collection yields.

Table 2. Summary of exa-cel clinical studies

Study ID	Study description ^a	Number of treated subjects ^b
111	Phase 1/2/3 Safety and efficacy in subjects with TDT Males and females with TDT aged 12 to 35 years (inclusive) Follow-up: up to 2 years after exa-cel infusion United States, United Kingdom, Italy, Germany, Canada BLA 125785/0 Enrollment completed	52
121	Main study for this BLA Phase 1/2/3 Safety and efficacy in subjects with severe SCD Males and females with severe SCD aged 12 to 35 years (inclusive) Follow-up: up to 2 years after exa-cel infusion United States, United Kingdom, Italy, Germany, Canada, Belgium, France Enrollment completed. Ongoing. Final report expected March, 2026. The Applicant initially submitted data with a data cutoff date (DCOD) on February 10, 2023 for interim analysis (IA) 2. The Applicant later submitted data with a new DCOD of June 14, 2023 for IA3, in the Day 90 update of efficacy and safety data for Studies 121 and 131.	42 (IA2) 44 (IA3)
131	Long-term follow-up (LTFU) study for a total of 15 years after exa-cel infusion for subjects treated in parent studies 111 (TDT), 141 (pediatric TDT), 121 (SCD), and 151 (pediatric SCD) after they completes or discontinues from the parent studies United States, United Kingdom, Germany, Canada, Italy	-

141	Phase 3 Safety and efficacy in subjects with TDT Males and females with TDT aged 2 through 11 years (inclusive) Follow-up: up to 2 years after exa-cel infusion United States, Italy Planned: 10 subjects (Protocol Version 2.1 [US], February 07, 2023)	0
151	Phase 3 Safety and efficacy in subjects with severe SCD Males and females with severe SCD aged 2 through 11 years (inclusive) Follow-up: up to 2 years after exa-cel infusion United States, Italy Planned: 10 subjects (Protocol Version 2.1 [US], February 08, 2023)	0
161	Phase 3b Safety and efficacy in subjects with TDT or severe SCD Males and females with TDT or severe SCD aged 12 to 35 (inclusive) Follow-up: up to 1 year after exa-cel infusion United States, Italy, Germany The primary objective is to assess HbF levels over time after exa-cel infusion Planned: 18 subjects (Protocol Version 3.1, April 21, 2023)	0

HbF: fetal hemoglobin; SCD: sickle cell disease; TDT: transfusion-dependent β -thalassemia

^a Except for the LTFU study (Study 131), all studies are ongoing single-arm studies where treated subjects received a single intravenous administration of exa-cel with a minimum recommended dose of 3×10^6 cells/kg

^b Number of treated subjects as of January 16, 2023 (Studies 111 and 141) and February 10, 2023 (Studies 121, 151, and 161). The applicant included data on two additional subjects treated in Study 121 in the Day 90 update with a cutoff date of June 14, 2023

Source: Adapted from - BLA 125787/0/8, Module 5.2, Table 5.2, including some information (e.g., planned sample size) from IND 18143.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was held on October 31, 2023, mainly to discuss suitable investigations into the theoretical and practical possibilities of unintended on-target and off-target DNA modifications. Please refer to the meeting website for more information. More information is available at <https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-october-31-2023-meeting-announcement-10312023>

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

The efficacy and safety database consists of data from Study 121, the main study, and the data from the SCD patients in Study 131, the LTFU study that include both SCD and TDT patients. Study 121 is a single-arm study that follows up each subject for a two-year duration after exa-cel infusion. Treated subjects will then enroll in Study 131 for a total F/U of 15 years post infusion. The review below will focus on IA3 in Study 121, with a DCOD of June 14, 2023, where 44 subjects were treated. Any information in Study 131 that may be relevant will be incorporated into this Section, as it provides continued F/U to those subjects treated in Study 121.

The Applicant reported in the AC meeting briefing document that Study 121 has completed enrollment and dosing, with 46 patients treated, and final data will be available the second half of 2025.

Reviewer Comment #2: Review content

I have rephrased various definitions (e.g., primary efficacy endpoint) and descriptions for clarity without changing the meaning. These rephrasing will not be separately pointed out. In addition, I will not evaluate information submitted for the sole purpose to support the accelerated approval (AA) pathway, i.e., the ICE and associated analysis set, as we will not consider the submission for AA. Some endpoints will be reviewed in detail by other review disciplines, and therefore will only be briefly mentioned here as needed. For example, HbF-related endpoints will be reviewed in detail by the clinical pharmacology reviewer, and platelet and neutrophil engraftment endpoints will be reviewed in detail by the clinical reviewer.

End of Reviewer Comment #2.

Reviewer Comment #3: Evolution of Study 121 protocol, statistical analysis plan (SAP), and challenges for review

Study 121 was titled “*A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects with Severe Sickle Cell Disease*”. There are more than 20 versions of the protocol over time for different regulatory authorities, including the FDA. I have summarized the evolution of the protocol and the statistical analysis plan (SAP) versions that are specific to the FDA in Table 3 below. This summary reveals the following salient features.

- The protocol started for a phase 1/2 study (Version 2.0, June 26, 2018) and went through multiple versions incorporating substantial revisions while subjects were

treated with exa-cel, including revisions in eligibility criteria, assessments, endpoints, and IA plan.

- Starting on protocol Version 6.9 (September 22, 2021), after 17 of the 30 subjects included in the primary efficacy set (PES) had been treated, the protocol was revised to be a phase 1/2/3 protocol, and an additional IA was added to an earlier time (n=10). Some of the revisions were adoption of FDA's recommendations that improved the trial design, e.g., change the primary efficacy endpoint from HbF responders to absence of severe VOCs (sVOCs). The last version of the protocol (Version 6.11, Sept 15, 2022) was revised to include ICE, which is irrelevant to this BLA review. My review of Study 121 will focus on protocol Version 6.11.
- The first SAP document (Version 2.0; September 23, 2021) submitted to IND 18143 was aligned with protocol Version 6.9. The SAP went through 4 more versions without being submitted to FDA. The next SAP submitted to FDA (Version 5.0; 26 Oct 2022) contained a substantial amount of critical design elements that can potentially bias trial results and that FDA disagreed with. At this time, 39 of the 44 subjects had been treated, including all 30 subjects that would be in the PES. The final SAP (Version 5.1; December 08, 2022) was submitted four months later to the BLA, but was never submitted to the IND. The Applicant claimed to have adopted all of FDA's feedbacks on SAP Version 5.0, except for the definition of platelet engraftment. This final version of SAP was submitted without tracked change. I have identified some features that FDA would not have agreed with if the SAP was submitted for review prior to the submission of the BLA.

The substantial changes in the protocol and SAP, when all subjects had been treated and part of the data had been known, poses challenges to the interpretation of trial results, in addition to the challenges that are usually associated with a single-arm trial. Some phrasings in the endpoint definitions are vague or prone to misinterpretation. These issues will be described in detail in the following Sections.

End of Reviewer Comment #3.

Table 3. History of Study 121 protocol, stand-alone statistical analysis plan (SAP), and meetings applicable to the FDA

Document Version Date	Notable revisions^a, discussions, and my comments, including # (%) SCD patients treated with exa-cel out of N=44
Protocol 1.0 Apr 13, 2018	Original Phase 1/2

Protocol 2.0 Jun 26, 2018	<ul style="list-style-type: none"> • Sample size: Up to 12 subjects with possible expansion to up to a total of 45 subjects • Primary efficacy endpoint: proportion of HbF responder ($HbF \geq 20\%$) • 2 IAs: $n=17$, $n=30$. O'Brien-Fleming (OBF) alpha spending. Null response rate 50%
Protocol 3.0, Dec 10, 2018	<ul style="list-style-type: none"> • Added to inclusion criterion #4 that pretreatment severe VOC events will be adjudicated by the Endpoint Adjudication Committee • Updated statistical analysis to include efficacy boundaries for the expanded study. Null response rate 60%. Remove OBF
Protocol 4.0 Sep 19, 2019	<ul style="list-style-type: none"> • Added $\beta S/\beta 0$ genotype • Updated initial number of subjects from 12 to 17 subjects • Updated exclusion criterion #7 so that subjects with ≥ 10 hospitalizations or emergency department visits in the year before screening that are consistent with chronic pain related to sickle cell disease are excluded • Clarified that subjects will be removed from the study if they have an important protocol deviation which compromises subject safety. <p>Note: This was submitted to Center for Drug Research and Evaluation (CDER) by mistake, and was later submitted to CBER IND 18143 amendment 53 on May 15, 2020.</p>
Protocol 5.0 Feb 04, 2020	<ul style="list-style-type: none"> • Added adolescent subjects (12 to <18 years) • Added that approximately 6 adult subjects will be dosed with exa-cel before conditioning and dosing of the first pediatric subject • Clarified that historical VOCs that occur within the 2-year period, including those which may begin just prior to the 2-year window and end during the 2-year window, will contribute to the determination of eligibility <p>Note: This was submitted to Center for Drug Research and Evaluation (CDER) by mistake, and was later submitted to CBER IND 18143 amendment 55 on May 15, 2020.</p>
Protocol 6.7 Jul 02, 2021	<ul style="list-style-type: none"> • Added $\beta S/\beta +$ genotype to the inclusion criteria • Clarified that historical VOCs (during the 2 years prior to screening) will be adjudicated by the EAC • Updated exclusion criteria to add that the subject must not have any risk factors that would increase the likelihood of busulfan-related toxicities and excluded subjects with positive hepatitis B surface antigen

	<ul style="list-style-type: none"> Removed reference to partial withdrawal of consent for subjects who do not enroll in the long-term follow-up study but consent to have their information collected through medical record review or telephone interviews <p>Note: Protocol Version 6.3 dated May 21, 2021 was withdrawn from US after FDA requested the sponsor to revert the neutrophil engraftment definition to the one prior to the revision made in protocol Version 6.3.</p> <p>A total of 16 subjects had received exa-cel by the time of protocol Version 6.3</p>
Protocol 6.9 Sep 22, 2021	<ul style="list-style-type: none"> Changed study from phase 1/2 to phase 1/2/3 Changed primary efficacy, key secondary efficacy, and secondary endpoints Changed statistical and interim analyses, including adding one early IA at n=10, and maintaining the sample size but changing the null response rate from 60% to 50% for a revised primary efficacy endpoint, adding new analysis set for primary efficacy endpoint, etc. <p>Note 17 subjects had been treated by this time. Some of the revisions, e.g., changing the primary efficacy endpoint from a biomarker to a clinical endpoint, is at the request of FDA.</p>
Protocol 6.11 Sep 15, 2022	Revision in this amendment include addition of intermediate clinical endpoint only, therefore this version of protocol is essentially the same as Version 6.9 for the purpose of this BLA review. By this time 36 subjects had been treated.
SAP 1.0 Dec 14, 2018	Not submitted to FDA
SAP 2.0 Sep 23, 2021	First SAP submitted to FDA (IND 18143 amendment 151) on Oct 22, 2021, under eCTD <i>Section 1.12 Other Correspondence</i> and requested FDA comments. Aligned with Protocol Version 6.9 (Sep 22, 2021)
SAP 3.0 13 Apr 2022	<p>Not submitted to FDA</p> <p>32 subjects treated.</p> <ul style="list-style-type: none"> Revised PES definition to include “<i>with the exception of those who receive RBC transfusions between Month 10 and Month 12 and have less than 14 months (including up to 2 months in Study 131) additional follow up time will be included in this set. In addition, subjects who die, discontinue the study, or continuously receive RBC transfusions for more than 12 months post CTX001 infusion will also be included in this set.</i>” Provided handling of subject death and discontinuation in PES

	<ul style="list-style-type: none"> Removed the strategy to address prohibited medications for efficacy analyses.
SAP 4.0 08 Jul 2022	<p>Not submitted to FDA</p> <p>No major change</p>
SAP 4.1 (US) 21 Sep 2022	<p>Not submitted to FDA</p> <p>35 subjects treated.</p> <p>I considered the revisions not relevant for the review of this BLA and omit them herein.</p>
SAP 4.2 (US) 12 Oct 2022	<p>Not submitted to FDA</p> <p>39 subjects treated.</p> <ul style="list-style-type: none"> Change to only include death(s) related to exa-cel in the PES
SAP 5.0 (US) 26 Oct 2022	<p>Submitted to IND 18143 amendment 199 (Oct 28, 2022) as part of a meeting package, including tracked changes compared to SAP Version 2.0, the last version of SAP that was submitted to FDA.</p>
SAP 5.1 (US) Dec 08, 2022	<p>Only submitted to BLA on Apr 03, 2023 without tracked changes, never submitted to IND 18143.</p> <p>41 subjects treated.</p> <p>The Applicant stated that changes were made to address FDA Written Response Only (WRO) feedback received Nov 28, 2022, with their response submitted to IND 18143 amendment 203 (Dec 22, 2022) and, in agreement with FDA, they reversed many of the changes that had been made in SAP Version 5.0:</p> <p><i>Specifically, Vertex agreed to incorporate all of FDA's comments/requests to the SAP (e.g., request for: a single data cutoff date for all subjects with SCD; handling of prohibited medications; restriction of response evaluation to parent study), except the platelet engraftment definition was not agreed upon; however, Vertex agreed to perform sensitivity analyses, reflecting FDA's position.</i></p> <ul style="list-style-type: none"> <i>Updated PES and EES definition to include Study 121 data only</i> <i>Removed "include up to 2 months in long-term follow-up Study 131" in primary efficacy and key secondary efficacy endpoints</i> <i>Added "subjects have received the prohibited medications for SCD (HU, L-Glutamine, Crizanlizumab, or Voxelotor) post CTX001 infusion, the prohibited medication treatment period will be excluded from the analyses for VF12, HF12, and VF9."</i>

Meetings	<p>There were 8 meetings with FDA meeting minutes issued, including Written Response Only (WRO) minutes. The discussions were extensive with multiple disagreements between the FDA and the sponsor, including some points that were repeatedly discussed without reaching an agreement. For brevity, I include below only select discussions that are most relevant to this review memo, and do not repeat discussion points that appeared in multiple meeting minutes.</p> <p>Type B Meeting. April 22, 2021. Meeting Minutes May 21, 2021:</p> <p><i>Post-meeting discussion: after further internal deliberation, FDA maintains the recommendation to include all VOC events [not just adjudicated severe VOC] in the definition of the primary efficacy endpoint, for the reasons elicited during the teleconference. In addition, FDA notes that study participants' pain symptoms are subject to filtering, thus not being referred to the endpoint adjudication committee, leading to undercounting of VOCs. Alternatively, FDA suggests that the sponsor consider conducting a controlled study, as was done in studies of crizanlizumab and hydroxyurea, which utilized similar definitions of VOCs.</i></p> <p><i>In addition, FDA maintains the recommendation to assess for the absence of VOCs [for] at least 24 months [instead of for at least 12 months] after a subject achieves a stable hemoglobin level. Robustness of the treatment effect, based in part on its durability for 24 months, would be important to weigh against any important safety issues that may be uncovered in the trial.</i></p> <p>...</p> <p><i>An endpoint which includes any VOCs is more clinically relevant for patients, and less susceptible to bias.</i></p> <p>...</p> <p><i>Study 121 enrolls a population with as few as 2 baseline VOCs/year, therefore a duration of 12 consecutive months free of VOCs is insufficient to demonstrate impact of CTX001, rather than chance. A meaningful period should last at least 24 consecutive months starting after subjects reach stable hemoglobin level. This would also be more informative of durability.</i></p> <p>WRO. May 17, 2022</p> <ul style="list-style-type: none"> FDA continued to recommend the sponsor to use a 24-month VOC free period for responder definition if a single-arm trial is used, instead of using the proposed 12 months duration, because the shorter duration cannot rule out response due to chance alone. One rationale is that the “data from prospective crizanlizumab SUSTAIN study where 17% of 66 subjects with SCD given placebo had zero VOCs during a 12-month observation period¹ (These subjects had baseline of ≥ 2 VOCs/year retrospectively assessed over a 1-year period before enrollment).” Another rationale is the
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inapplicability of the retrospective Medicaid claims data provided by the sponsor: *“it appears that your retrospective study permitted broad definitions of SCD diagnosis codes for identifying events suggestive of VOCs ... Thus, there are discrepant criteria of enrollment/VOC definition between the retrospective Medicaid study vs. study 121 ... decrease our confidence in the VOC remission rate you calculated.”*

- Sponsor stated: *“The Sponsor will demonstrate that the current VOC definition used in Study 121 is broad, inclusive of, and objectively defined for all VOC events, and includes terms included in the endpoints “all VOC/other VOC” in other clinical trials that have been conducted in SCD. To further support analyses of VOC, the Sponsor proposes to also provide additional analyses of episodes of pain from reported AEs (both serious and non-serious) and provide that as supportive evidence in the planned BLA.”* FDA agrees with this approach.

Pre-BLA Meeting. August 9, 2022. Meeting Minutes September 8, 2022

- FDA continued to recommend a BLA submission with 40 subjects with SCD followed for ≥ 18 months.
- FDA stated: *“Because of the single-arm design of Study 121, and proposed baseline severity of the SCD subjects, while we have recommended a 24-month observation period to monitor for VOs to inform of efficacy, we may consider the primary endpoint assessment at a minimum 18 months to 24 months following administration of the investigational product; however, this would be a review issue.”*
- FDA stated: *“The sponsor further added that they were planning to seek an indication that included adolescent patients and asked FDA for comment regarding this subpopulation. FDA noted that the data on adolescent subjects comprised only a fraction of the total studied population, and while we have no specific objection to inclusion of adolescents in the sought indication, adequacy of data would be a review issue for the BLA submission.”*

WRO. November 28, 2022

- FDA stated: *“No, we do not agree. ... We understand that you are planning to submit your BLA at the time of Interim Analysis 3 [for TDT and IA2 for SCD], and you then propose to include additional efficacy data collected after the BLA data cutoff and before the Day 90 data cutoff. The number of subjects and months of follow up that would comprise the late dataset is unclear. At the time of BLA submission, you should have a comprehensive data package that will allow us to assess efficacy. We cannot agree with a late component for efficacy. We continue to request that you come in with a*

	<p><i>minimum of 45 subjects with ≥ 18 months of follow up for each disease [SCD and TDT].”</i></p> <ul style="list-style-type: none"> • Comments on SAP Version 5.1 submitted as part of the meeting package. Some comments focused on the TDT trial and then stated the the comment also applied to the SCD trial, I modified slightly to focus comments on Study 121, the SCD trial. The <ul style="list-style-type: none"> ○ FDA do not agree with the proposal to have a later data cutoff date for the 3 adolescent subjects than the one for adult subjects. ○ FDA do not agree with the proposal to remove “<i>The prohibited medication treatment period will be excluded in the analysis of the primary efficacy endpoint.</i>” statement that was in a previous version of SAP. ○ FDA stated: “[FDA] do not agree with your proposal to exclude from SCD study 121 PES those who receive RBC transfusion between Month 10-12 and have <14 months of additional follow up time, as this would enrich the proportion of successful subjects and bias outcome.” ○ FDA do not agree with the proposal to add more flexibility to the definition of responders, including extending the efficacy evaluation period beyond 24 months into the LTFU study (Study 131) if a subject could not achieve at least a 12-month period of being free of severe VOC within the 24-month F/U withing Study 121. ○ FDA do not agree with the sponsor’s proposal to carry the VOC free status forward to 24 months “<i>if a subject dies or is discontinued from the study before achieving VF12 ... due to reasons other than CTX001-related adverse events without experiencing graft failure.</i>” ○ FDA stated: “<i>In the SAP, you state "If an IA is not conducted, alpha planned for this IA will be recovered for the subsequent analysis," please provide more details on the proposal and clarify the success boundaries for the primary efficacy endpoints you will use to support the BLAs.</i>” <p>IND 18143 amendment 203 submitted December 22, 2022. Sponsor’s response to FDA’s WRO dated November 28, 2022</p> <p>To save space, the review of the response will be included in the corresponding sections below.</p>
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^a The table only includes the revisions that are relevant to this BLA review, which is a small portion of the substantive revisions in the protocol and SAP.

Source: Reviewer’s summary based on information in the BLA and the IND, including Applicant’s response to reviewer’s information request regarding the history of the protocol and SAP.

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective

Evaluate the safety and efficacy of a single dose of exa-cel in subjects with severe SCD

Secondary Objectives

- Assess the effects of exa-cel on disease-specific events and clinical status
- Quantify gene editing efficiency

6.1.2 Design Overview

Study 121 is a single-arm, single-dose, multi-site, phase 1/2/3 study in subjects with severe SCD. The study planned to treat 17 to 45 SCD subjects, 12 to 35 years of age, inclusive. Subjects were to undergo mobilization and apheresis collection of CD34+ cells for manufacture of autologous exa-cel, followed by myeloablative conditioning and infusion of exa-cel. Subjects were then to receive RBC transfusions for post-transplant support and SCD management and be followed up for 24 months after exa-cel infusion to be assessed for efficacy and safety endpoints. The F/U schedule was monthly for the first 6 months, and then every 3 months thereafter until Month 24. All subjects who receive exa-cel will be asked to enroll in the LTFU study, Study 131, after completion or withdrawal/discontinuation from Study 121, for a total F/U of up to 15 years after exa-cel infusion. The F/U schedule in Study 131 is every 3 months until the end of Year 3 after exa-cel infusion, every 6 months for Year 4 and Year 5, and annually thereafter. Study 121 started with adult subjects and later expanded to include adolescent subjects after the Data Monitoring Committee reviewed initial data in the treated adult subjects. The primary efficacy analysis is the proportion of subjects achieving at least a 12-month period without any severe VOCs within the 24-month F/U in Study 121, compared to a 50% null response rate.

6.1.3 Population

Key inclusion criteria in original numbering as in the protocol:

2. Subjects 12 to 35 years of age, inclusive, on the date of informed consent
3. Documented genotypes of $\beta S/\beta S$, $\beta S/\beta 0$, or $\beta S/\beta +$
4. Subjects with severe SCD. Severe SCD is defined by the occurrence of at least 2 of the following events per year during [each year of] the 2-year period before screening, while receiving appropriate supportive care (e.g., pain management plan, HU):

- Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or RBC transfusions
- Acute chest syndrome, 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 hemoglobin concentration of ≥ 2 g/dL.

Historical severe VOCs will be 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 subjects 12 to 16 years of age
6. Karnofsky performance status of $\geq 80\%$ for subjects ≥ 16 years of age or Lansky performance status of $\geq 80\%$ for subjects <16 years of age
7. Eligible for autologous stem cell transplant as per investigator's judgment

Key exclusion criteria in original numbering as in the protocol:

1. An available 10/10 human leukocyte antigen-matched related donor
5. Treatment with regular RBC transfusions that, in the opinion of the investigator, cannot be interrupted after engraftment
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, are 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 subjects 12 to 18 years of age

Baseline period for sVOCs is defined as two years prior to enrollment, e.g., signing informed consent form and being determined to have met the eligibility criteria. All sVOCs, pre- or post-exa-cel infusion (up to 24 months), were planned to be adjudicated by the EAC.

Endpoint Adjudication Committee:

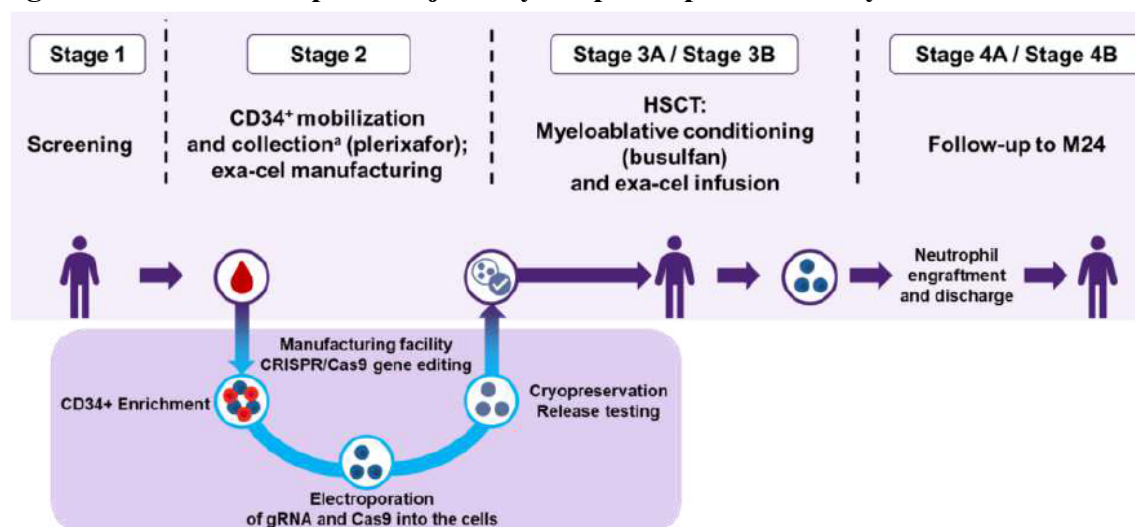
From the protocol: *The Endpoint Adjudication Committee (EAC) will be composed of an independent, external group of experts with appropriate clinical and scientific background to evaluate VOCs. The EAC will be adjudicating historical VOCs (during the 2 years prior to screening) and on-study VOCs to ensure that the events meet the study's definition of a severe VOC. Historical VOCs that occur within the 2-year period prior to screening, including those which may begin just prior to the 2-year window and end during the 2-year window, will contribute to the determination of eligibility. For subjects with one or more rescanning, all severe VOCs that occurred during the 2 years before the last rescanning date will be adjudicated. The EAC will adjudicate historical VOCs to ensure that the number of historical VOCs are sufficient for eligibility. Details of the EAC structure, function, and process will be included in the EAC charter.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

As an *ex vivo* gene-targeted approach, exa-cel treatment amounts to a bone marrow transplantation with modified autologous cells. A participant's journey, including study treatments, in Study 121 is summarized in Figure 1. The journey consists of 4 stages:

- 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 periods. The duration of Stage 1 will be approximately 2 to 4 months.
- Stage 2: mobilization with plerixafor, autologous CD34+ cell collection via apheresis, and exa-cel manufacture. The duration of Stage 2 will be approximately (b) (4).
- Stage 3: myeloablative conditioning with pharmacokinetically adjusted busulfan for 4 consecutive days, followed by exa-cel infusion (Study Day 1). Exa-cel is administered as an intravenous suspension consisting of a minimum of 3×10^6 CD34+ cells/kg body weight in a cryopreservation solution containing 5% dimethyl sulfoxide. The duration of Stage 3 will be approximately 1 month.
- Stage 4: in-hospital F/U until neutrophil engraftment, followed by outpatient F/U for approximately 2 years after exa-cel infusion. During this period, participant will continue to receive RBC transfusion for post-transplant support or for SCD management as deemed necessarily.

Figure 1. Schematic of planned journey for participants in 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.

Source: The Applicant's Advisory Committee Meeting Briefing Document, Figure 7, p.50

6.1.6 Sites and Centers

Table 4 summarizes the number of enrolled subjects and clinical sites by country. A total of 63 subjects enrolled at 14 sites, with the majority of subjects enrolled (47/63, 75%) and treated (35/44, 80%) at United States of America (USA) sites.

Table 4. Enrolled subjects and clinical sites by country in Study 121 (N=63)

Country	Number of clinical sites	Number of enrolled subjects	Number of exa-cel treated subjects
United States of America (USA)	8	47	35
Italy (ITA)	1	7	6
Belgium (BEL)	1	3	2
Canada (CAN)	1	2	1
Great Britain (GBR)	1	2	0

Germany (DEU)	1	1	0
France (FRA)	1	1	0

Source: Reviewer's analysis

6.1.7 Surveillance/Monitoring

In Study 121, subjects will be followed up monthly until Month 6 after exa-cel infusion, and every 3 months until Month 24. Subjects who complete the planned 24-month F/U or discontinue early in Study 121 will be asked to enroll in the LTFU study, Study 131, for a total F/U of up to 15 years after exa-cel infusion. In Study 131, The F/U frequency is every 3 months until end of Year 3, every 6 months for Year 4 and Year 5, and then annually thereafter until up to Year 15.

6.1.8 Endpoints and Criteria for Study Success

Day 1 is the day of exa-cel infusion. In the application, the Applicant defines month as 30 days. I may use 30.4 days (365/12) as a month in some calculation following convention. The difference between these two approaches is trivial.

Primary efficacy endpoint: Proportion of VF12 responders

The primary efficacy endpoint is the proportion of VF12 responders, i.e., patients who have not experienced any sVOC for at least 12 consecutive months after exa-cel infusion during the 24-month F/U in Study 121. The following conditions are required to be satisfied simultaneously in the definition of a VF12 responder:

- A VF12 responder's sVOCs free period can be any 12 consecutive months within the 24-month F/U period in Study 121, and sVOCs experienced outside of the 12-months window, i.e., the other 12-month period, do not affect the VF12 responder status. For example, a subject is considered a VF12 responder if they are free of sVOC from Months 7 to 18, inclusive, while experiencing sVOCs any time outside of this window would not change the responder status. Or a VF12 responder could be free of sVOC during Months 13 to 24, inclusive, and experiencing sVOCs outside of this window.
- Evaluation period for the VF12 responder status starts 60 days after the last RBC transfusion for post-transplant support and SCD management. Completion of the (initial) RBC transfusions is determined when all those transfusions for post-transplant support and SCD management have finished. By "last" the Applicant means any RBC transfusion during the first 10 months after exa-cel infusion, including those for treating sVOCs, because the subject might still achieve VF12 responder status if they are sVOC free from Month 13 to Month 24, inclusive.
- Patients must have ≥ 16 months of F/U to be evaluated for VF12 responder status.

The SAP version that was only submitted to the BLA had the following additional considerations in the definition of VF12 responders:

- *For subjects who have received the prohibited medications for SCD (HU, LGlutamine, Crizanlizumab, or Voxelotor) post CTX001 infusion, the prohibited medication treatment period will be defined as the period from the first dose of the prohibited medication to 3 months after the last dose of the prohibited medication. The prohibited medication treatment period will be excluded in the analysis of the primary and key secondary efficacy endpoints. After CTX001 infusion, the VOC free period occurring before and after the prohibited medication treatment period will be considered consecutive unless an adjudicated severe VOC occurs during the prohibited medication treatment period.*
- *If a subject has died or discontinued the study before achieving VF12 starting at least 60 days after the last RBC transfusion for post-transplant support or SCD management due to reasons other than CTX001-related adverse events, then the VOC free status of the subject will be carried forward up to 24 months post CTX001 infusion.*
- *Subjects who die or discontinue the study due to CTX001-related adverse events before achieving VF12, or continuously receive RBC transfusion for post-transplant support or SCD management post CTX001 infusion after Month 10 will be considered non-responders for VF12.*
- *EAC will adjudicate all potential severe vaso-occlusive crisis (VOC) events reported by investigators from two years prior to consent /rescreening through fifteen years following CTX001 infusion and adjudicating whether the event satisfies the definition of severe VOC as per Study 121 protocol.*

Study success criterion based on the primary efficacy endpoint of proportion of VF12 responders

The Applicant set the null hypothesis on the VF12 response rate at 50%. That is, the hypothesis tested for the VF12 endpoint was

$$H_0: \pi \leq 50\% \quad \text{versus} \quad H_1: \pi > 50\%,$$

where π is the proportion of VF12 responders, i.e., being free of sVOCs for at least 12 months within the 24-month efficacy evaluation period.

This null response rate was used in planning the sample size and interim analyses.

Reviewer Comment #4: Primary efficacy endpoint VF12 response rate

The definition of VF12 response in this submission is unusual by using an extensive degree of flexibility to achieve “response”, compared to some definitions that are more commonly used, i.e., being free of events during a fixed period (Months 7 to 18,

inclusive). The phrasing of the definition is also vague and potentially misleading by not mentioning the degree of flexibility associated with the response. I will describe below this concern in the context of FDA's interaction with the Applicant during the evolution of the definition of the VF12 response during the IND stage.

In FDA's April 22, 2021 meeting with the IND sponsor, FDA recommended the primary efficacy endpoint to be defined as: *"proportion of subjects infused with CTX001 who after achieving stable hemoglobin level have no VOC for at least 24 consecutive months."* FDA provided the following rationales for the recommendations, some of which specifically addressing potential biases in single-arm trial, with a suggestion of alternatively using a controlled trial.

- The 24-month duration in the response definition was requested to have adequate durability in comparison to HSCT with suitable donors, a curative therapy for SCD, because the risks of the exa-cel treatment regimen include those associated with HSCT procedures, and additional exa-cel specific safety issues that may be uncovered in the trial. Exa-cel's potential risks of unintended DNA modifications is not feasible to be fully studied pre-marketing and will continue to be studied post-marketing.
- All VOC, not just the sVOC as defined in the protocol, was more relevant to patients and less subject to biases in a single-arm trial where investigators may filter out what VOCs will go to the EAC for adjudication.
- FDA recommended that the response be evaluated with a fixed starting timepoint, i.e., when stable hemoglobin levels are achieved.

However, while the Applicant designed Study 121 as a 24-month trial, the VOC-free duration in the responder definition was considerably shortened to be 12 months. And only protocol defined sVOC, not all VOC, are included in the definition. Both of these changes from FDA's recommendations increase the null response rate to an unknown extent. Furthermore, the VF12 response definition includes multiple sources of flexibility that are not apparent from the phrasing of the definition, which further increase the null response rate considerably. Below is a summary of these flexibilities.

- The definition of VF12 response does not mention that the 12-month sVOC-free duration can be flexibly achieved within a 24-month evaluation period. It may be misinterpreted as meaning an effect of at least 12 months of sVOC-free period starting from the time exa-cel takes effect. Figure 2 illustrates, schematically, the substantial difference between a commonly used response criterion of having response during a fixed-period of 12 months (e.g., Months 7 to 18, inclusive) and the Study 121 criterion of having response flexibly during any 12-month period out of a 24-month F/U. With the fixed-period criterion, only scenario (C) is a response while the other 4 scenarios, including an unlimited number of scenarios denoted by the dots, are non-response. However, with the Study 121 flexible-period criterion, all 5 scenarios and an unlimited number of scenarios (denoted by

the dots) with any period of at least 12 consecutive months of being sVOC free will be VF12 response. The difference in null response rate between these two responder definitions is substantial: when the null mean sVOC rate is 2 events per year, the null response rate is 13.5% vs. 40.6% for the fixed-period and the Study 121 VF12 response definition, respectively, when calculated based on a Poisson process. The null response rates are 5.0% (fixed-period criterion) vs. 19.9% (flexible-period criterion) when the mean sVOC rate is 3 events per year. Thus, the flexible-period response definition in Study 121 inflates the null response rate to 3 times and 4 times that of the commonly used fixed-period response definition, under two sVOC mean rates that are represented in Study 121 eligibility criteria. Table 5 lists the null response rates of these two response definitions under more scenarios, for mean sVOC rates ranging from 2 per year to 10 per year. For the evaluation period out of which the Study 121 flexible-period 12-month response can be claimed, I have included results for 18-month and 20-month, in addition to 24-month (the full evaluation period). The 18-month is included because some other clinical development programs in one-time treatment for chronic conditions, including SCD, used a fixed-period response from Months 7 to 18 (inclusive) after the products were thought to have taken effect. The 20-month period is included as the Applicant stated that subjects would need about 2 months of RBC post-exa-cel infusion and 2 additional months would be used to allow washout before evaluation of treatment effect. The null response rate is considerably inflated with a flexible-period response compared to a fixed-period response, with more inflation when the flexibility period is longer. The degree of inflation increases with mean sVOC rates; 3 times higher when mean sVOC is 2 per year and 4 times higher when the mean is 3 per year. When mean sVOC is ≥ 6 per year, the inflation is inconsequential as the null response rate is less than 2% regardless of the response criterion. However, note that this table only looks at one single factor: flexibility due to the extended evaluation period. I will describe further considerations for the null response rate later. To be transparent, the VF12 response could be termed VF12/24 to reflect the flexible evaluation period.

- Late in the clinical development program, the Applicant proposed allowing achievement of a VF12 response to include up to an additional 2 months of data in the LTFU Study 131, potentially further increasing flexibility in the definition of VF12 response. This in effect extends the period during which a 12-month sVOC-free duration can be located from 24 months to 26 months. The Applicant ultimately agreed to forsake this proposal at FDA's advice.
- Another source of flexibility in the VF12 response definition comes from the choice of starting point for the efficacy evaluation. The evaluation starts after a 60-day washout of the "last" RBC transfusion for post-transplant support or SCD management. On the surface, this requirement is consistent with FDA's initial recommendation. However, FDA's recommendation regarding RBC transfusion

was in the context of establishing a starting time that is not as flexible as the VF12 definition, e.g., HbF level reaching steady state. As discussed below, exa-cel HbF steady states were reached by most subjects much earlier than Month 4, which would put the start time for efficacy evaluation no later than start of Month 7 even allowing for RBC transfusion support and washout. The Study 121 VF12 response allows “last” RBC transfusion as late as the end of Month 10, including transfusions for treating sVOCs. Any sVOC occurring before Month 11 would not count toward the VF12 response determination if an RBC occurs later than those sVOCs. This is another flexibility in the VF12 response definition compared to a fixed-period response definition, and its impact is difficult to gauge.

- The Applicant stated that “*A period of 16 months was chosen to capture ~2 months of RBC transfusions after exa-cel infusion, a 60 day washout period, and an efficacy assessment period of 12 months.*” However, a minimal F/U of 16 months is neither sufficient nor necessary to determine VF12 response status in some situations, e.g., a subject who experiences any sVOCs during Months 13 to 15 would not need additional F/U to determine that this subject is not a VF12 responder. This is another source of flexibility that could lead to excluding non-response from analysis sets.
- Another source of flexibility in the VF12 response definition comes from how prohibited medication was planned to be handled. While the Applicant stated they had incorporated FDA’s recommendation on excluding the prohibited medication treatment period from the analysis of the primary and key secondary endpoints for Study 121 if a subject receives any prohibited medications after exa-cel infusion, they added the additional stipulation to the SAP in the BLA (Version 5.1, Dec 8, 2022) that “*the VOC free period occurring before and after the prohibited medication treatment period will be considered consecutive unless an adjudicated severe VOC occurs during the prohibited medication treatment period.*” This addition was not reviewed by FDA and is not appropriate. Use of prohibited medication should restart the efficacy evaluation period for the VF12 response.
- At the FDA’s request, the Applicant added that subjects who die or discontinue the study due to exa-cel-related adverse events before achieving VF12 will be considered non-responders for VF12. Note that “exa-cel related” means the entire exa-cel transplant regimen, including myeloablative conditioning.
- The Applicant stipulated that death or discontinuation due to reasons other than exa-cel related adverse events would be imputed up to 24 months with VOC free status prior to these intercurrent events. This approach is not appropriate.

The unique definition of VF12 responders in this submission complicates interpretation of treatment effect, as it is quite distinct from a natural interpretation that the 12 months of sVOC-free period would start at the time the treatment takes effect by using a flexible starting point of the period. This also complicates the choice of a reasonable null

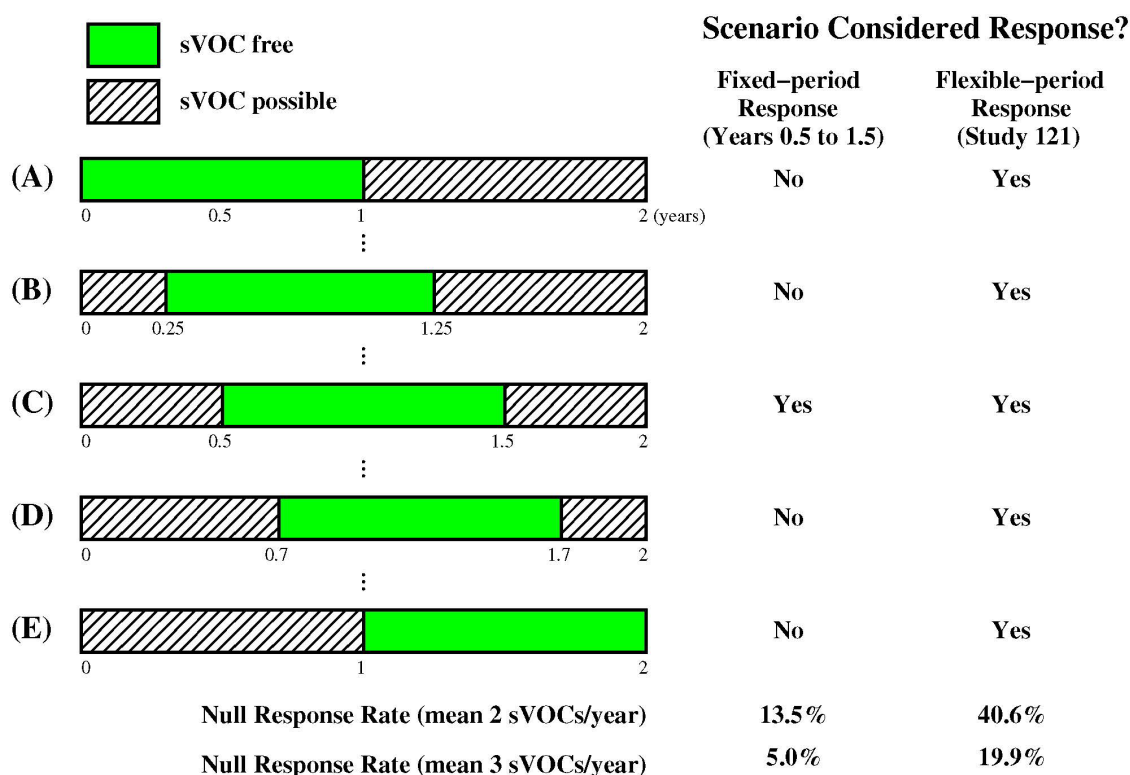
response rate to account for the multiple sources of flexibilities in the definition and potential biases in single-arm trials. This latter issue, in turn, highlights the potential of the definition to mislead users of the product in understanding the true magnitude of the treatment effect. I will discuss this topic in the next reviewer comment.

In addition, there appears to be a lack of a standardized and structured approach to ensure all VOCs were recorded by the study subjects and were reported to the investigators. The “SCHEDULE OF ASSESSMENTS” in the protocol did not include any information on specific, active inquiries about VOCs, e.g., journals/diaries kept by study subjects and/or questionnaires used by investigators/staff to elicit VOC information. In response to FDA’s IR about the VOC collection approach, the Applicant made the following statement:

The identification of VOCs by the investigators is a continuous process throughout a subject’s time in the clinical study. All potential VOCs (historical and on-study events) were identified by investigator/site staff at study visits and other timepoints via medical record review, as well as by subject notification of an event to the investigator/site staff. Investigators relied on institutional medical records, and if needed, received access (with subject consent) to medical records from the subject’s physicians, including those outside the study site institution.

This statement does not address instructions given to trial participants regarding reporting of VOCs, nor does it document active solicitation of VOCs at encounters with investigators. As such, there remain potential biases due to under-reporting of sVOCs after exa-cel treatment.

Figure 2. Illustration of the substantial difference between a commonly used fixed-period response criterion and the flexible-period response criterion used in Study 121



Note: This graph uses year, instead of month, as unit for easier annotation. The commonly used fixed-period response criterion is being sVOC free from Year 0.5 to 1.5, i.e., Month 7 to Month 18, inclusive. The Study 121 flexible-period response criterion is being sVOC free for any consecutive one-year period within the 2-year F/U period. The null response rate is calculated based on Poisson process.

Source: Reviewer's analysis

Table 5. Null response rates of fixed-period and Study 121 flexible-period response definitions, both for a 12-month response duration

Mean sVOC rate under the null (sVOCs/year)	Null response rate (%): Fixed-period	Null response rate (%): Flexible-period out of 18 months	Null response rate (%): Flexible-period out of 20 months	Null response rate (%): Flexible-period out of 24 months
2	13.5	27.1	31.7	40.6
3	5.0	12.4	15.0	19.9
4	1.8	5.5	6.7	9.1

5	0.7	2.4	2.9	4.0
6	0.2	1.0	1.2	1.7
7	0.1	0.4	0.5	0.7
8	0.0	0.2	0.2	0.3
9	0.0	0.1	0.1	0.1
10	0.0	0.0	0.0	0.0

Note: The null response rate is calculated based on Poisson processes under the given sVOC mean rates. In addition to the full 24-month evaluation period, an 18-month evaluation is also investigated, as in some other clinical development programs the fixed-period evaluation is from Months 7 to 18 (inclusive) to allow the product to start taking effect and thus the Study 121 flexible-period would be out of 18 months compared to those programs. A 20-month evaluation period is also investigated as the Applicant stated that subjects took about 2 months to stop RBC transfusion and would exclude 2 months after last RBC transfusion for washout from the efficacy evaluation period.

Source: Reviewer's analysis

End of Reviewer Comment #4.

Reviewer Comment #5: Evaluating the choice of the null response rate on VF12 responders

The Applicant set the null response rate for VF12 response at 50%. I requested that rationales for this choice be provided, which should take into consideration factors that may influence the null response rate, e.g., subject characteristics, definition of the analysis set and the endpoint. The Applicant submitted a response to my request in BLA 125787/0/66 on September 28, 2023.

None of the rationales considers the impact of the flexibilities in the VF12 response definition I discussed in “Reviewer Comment #4”, i.e., all the endpoints discussed in the rationales are fixed-period endpoints, different from the VF12 response definition. In what follows I will first summarize my evaluation of each of the three rationales provided by the Applicant (Figure 3), and then incorporate the impact added by the flexibility in the VF12 response definition.

The first rationale provided was that the 3-year event free survival, with event defined as graft failure, was around 50% in SCD patients aged ≥ 13 years who underwent allogeneic HSCT between 2008 and 2017 from donors that were not matched siblings (Brazauskas et al. Blood. 2020;136(5):623-26). The data consisted of 337 SCD patients, including those aged ≤ 12 years. The paper did not provide the breakdown of the two age groups, though in the larger dataset used in the paper 40% were aged ≥ 13 years. The Applicant included this source “because it reflects outcomes of allogeneic HSCT as a treatment

with curative intent for patients with sickle cell disease (SCD) without a matched related donor,” which is relevant in that FDA previously recommended aiming for an effect size similar to allogeneic HSCT given that the risks of the exa-cel treatment regimen at least includes those for autologous HSCT.

My evaluation of rationale #1. The 3-year EFS endpoint and the Study 121 VF12 response endpoint have nothing in common in their definitions, therefore this source of data is not relevant to the evaluation of the appropriateness of the null VF12 response rate. In addition, the Applicant did not provide information on whether the patients in the HSCT paper are comparable to Study 121 subjects at baseline.

The second rationale provided is based on a retrospective cohort analysis of data on 71,907 patients with SCD between January 01, 2000 and December 31, 2014 in the Medicaid claims databases, to assess the proportion of SCD patients observed to have absence of VOCs throughout the study follow-up (VX21-SCD-002 clinical study report in BLA Module 5.4, Date of Report: October 19, 2022). Diagnosis codes associated with the delivery of healthcare and pharmacy claims were used to identify patients, characteristics, and outcomes of interest. The Applicant reported that the 12-month VOC-free rate during the 1-year F/U was 9.1% [95% confidence interval (CI): 8.4%, 9.9%] among the 5,874 SCD patients identified to have ≥ 2 VOCs in each year of a 2-year baseline period, and was 16.6% [95% CI: 15.8%, 17.4%] among the 9,174 SCD patients identified to have ≥ 2 VOCs in a 1-year baseline period. For the latter analysis, selection criteria were based on the placebo group from the SUSTAIN study (See SUSTAIN study description below in the 3rd rationale). There are considerable dissimilarities in the baseline characteristics and assessments between the Medicaid study patients and the Study 121 subjects, causing difficulty in extrapolating the Medicaid study results to Study 121. Some, but not all, dissimilarities are listed below.

- The Medicaid study had 43% adolescents, compared to 23% (7/31) in Study 121.
- For the Medicaid study, VOCs were identified using International Classification of Disease Codes (ICD) diagnosis codes in hospitalization and emergency department visit claims. For Study 121, a severe VOC is defined as meeting any of the 4 categories listed previously and was reported by the investigators to the EAC and adjudicated by the EAC. This affects both comparability in baseline characteristics and the response definition post-baseline. Furthermore, at least some of the eligibility criteria in Study 121 were not applied to the Medicaid study. For example, Study 121 excluded patients with significant chronic pain or acute exacerbations of chronic pain in the investigators' judgment and did not count those in the sVOC events in F/U, but the Medicaid study did not use these procedures.
- The Medicaid study was for earlier times (years 2000 to 2014) compared to Study 121 with first patient enrolled on November 27, 2018. There is a trend towards higher response rate in more recent time within the Medicaid study itself; the 5-

year period from 2010 to 2014 reported a higher 12-month VOC-free rate (13.1%) than the earlier 3-year period (2002-2004, 6.4%) and 5-year period (2005-2009, 11.0%). For patients having multiple years of data in the databases, the Medicaid study used the earliest time for those patients and therefore reports the lowest response rate estimate out of all the possible estimates. For example, the patient cohorts for the response rate estimate for the three periods 2002 to 2004, 2005 to 2009, and 2010 to 2014 account for 49.4%, 32.5%, and 18.1% of total data, respectively.

My evaluation of rationale #2. The Applicant's estimate of a 9.1% 12-month VOC-free response rate in the Medicaid study likely underestimates the Study 121 VF12 null response rate to an unknown extent, due to several factors in the Medicaid study that differ from Study 121: (1) Not capturing VOCs that are managed in outpatient care setting; (2) lack of details of clinical assessments and the results as in investigative studies; (3) placing more weight in "older" data when more recent data would have given a higher response rate, in addition to the general limitations associated with claims data. This rationale was previously reviewed and discussed by FDA in the May 17, 2022 meeting. In the meeting minutes, FDA summarized the limitation of the Medicaid study and FDA's lack of confidence in the applicability to Study 121 of the response rate reported in the Medicaid study.

The third rationale is based on the crizanlizumab/SUSTAIN Study, a double-blind, placebo-controlled trial assessing the safety and efficacy of crizanlizumab in SCD patients [Ataga KI *et al.* N Engl J Med. 2017;376(5):429-39]. The Applicant calculated that, based on the Ataga *et al.* paper, the 12-month VOC-free rate after crizanlizumab treatment was 17% [95% CI: 8.8%, 28%] in the placebo arm (N=65). These patients had ≥ 2 VOCs in the one year prior to entering the trial, with 37% with ≥ 5 VOCs/year compared with 21% (N=44) in Study 121. The Applicant stated that the 17% placebo response rate in the SUSTAIN Study would overestimate the Study 121 VF12 null response rate (if it is defined as fixed-period), because Study 121 required subjects to have ≥ 2 sVOCs for each of the two years prior to trial enrollment while the SUSTAIN Study required ≥ 2 VOCs for only one year prior to trial enrollment. However, SUSTAIN Study appeared to have more severe subjects (e.g., more subjects with ≥ 5 VOCs/year). It is difficult to know whether 17% is an overestimate when all the differences between the two studies are considered. In addition, the upper limit of the 95% CI on the SUSTAIN Study is 28%.

My evaluation of rationale #3. Of all the three rationales provided, the placebo arm response rate (17%, 95% CI: 8.8%, 28%) in the clinical study in rationale #3 appears to be most relevant to estimate the Study 121 VF12 response rate, given the overall similarity between the baseline characteristics and possible qualitative adjustment for dissimilar factors.

Taken together, the best estimate of a null response rate in Study 121, if response is to be defined as a fixed-period endpoint of 12 months free of sVOCs (e.g., Months 7 to 18,

inclusive) and there are little biases from the single-arm design, would be around 17%. However, as discussed under **Reviewer Comment #4**, VF12 response was defined as being sVOC free in any 12 consecutive months during the 24-month F/U. This flexible-period definition inflates null response rates several folds compared to the fixed-period definition. In what follows, I estimate the null response rate for VF12 as defined in Study 121 by incorporating the considerations of flexible-period factor into the fixed-period response rates derived from the Applicant's three rationales above (i.e., around 17%).

Adding in the impact of the flexibility in the flexible-period VF12 response definition

The inflation of null response rate in a flexible-period response definition increases with the length of the F/U period (Table 5). For example, an 18-month F/U period increases the null response rate to be 2 times (27.1%/13.5%) of the fixed-period response rate if the baseline sVOC rate is 2 per year. This inflation factors are 2.3 and 3 times for 20-month and 24-month F/U, respectively. When the baseline rate is 3 sVOC/year, the inflation factors are 2.5, 3, 4 times for the three F/U periods, respectively. As the Applicant expected efficacy evaluation to start after 4 months post exa-cel treatment, I will use the 2.3 inflation factor. **Therefore, the best estimate of a VF12 null response rate is 17% \times 2.3 = 39%, with considerable remaining uncertainties.** The remaining uncertainties, which most likely will increase the null response rate further, stem from the additional, less quantifiable flexibilities in the VF12 response definition, exclusion of sVOCs due to chronic pain, and the single-arm design.

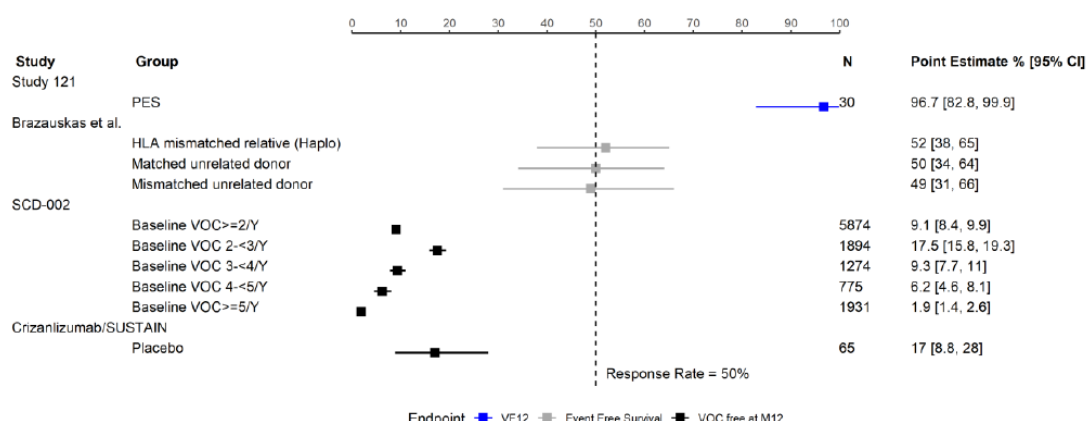
The Applicant acknowledged that the extended F/U period used to allow achievement of VF12 response would increase the null response rate, but did not provide any related investigation by simply stating that the 50% threshold they chose "*far exceeds*" all the estimates reported in the three rationales. It is judicious, as the Applicant seemed to indicate, to choose a null response rate much higher than any initial estimates to account for less quantifiable biases likely present in single-arm trials. **Taken into account all the considerations, including the three rationales, the flexibility inflation factor, and remaining uncertainties, I do not believe that 50% likely represent a threshold that is higher than the true null response rate in the Study 121 VF12 endpoint.** In view of the high level of uncertainties with the null response rate, I recommend reporting VF12 endpoint results in confidence intervals only, and not reporting a p-value of test against a null of 50%.

Technical note #1. Another estimate of a fixed-period null response rate would be a weighted average of the fixed-period response rates from Table 5 column 2, with weights being the baseline sVOC rates in Study 121. This estimate would be quite small given the range of the baseline sVOC rates in Study 121. However, this approach would be erroneous as Table 5 is a purely theoretical calculation based on a Poisson process, without reflecting trial conditions. The 17% placebo response rate in the crizanlizumab/SUSTAIN Study, with similar baseline VOC rates as in Study 121, illuminates this point. Nevertheless, Table 5 accurately reflects the response rate inflation

introduced by flexibilities in the F/U period, and has been used as such in leading to my conclusion above.

Technical note #2. The time for last RBC in the 30 PES subjects in Study121 ranges from Study Days 11 to 52 (Months 0.4 to 1.7) with a median of 0.6 months, and 80% of subjects had the last RBC no later than Month 1.0. Using Month 1.0 as the last RBC time would leave 21 months during which VF12 can be achieved, which results in an inflation factor of 2.5, and put the best estimate as $17\% \times 2.5 = 42.5\%$ instead of the 39% estimated with a 20-month efficacy evaluation period I discussed above prior to seeing the data. Nevertheless, the 20-month calculation above has illustrated the issue adequately.

Figure 3. Applicant's three rationales for supporting a null response rate of 50% for the VF12 endpoint: Allogeneic HSCT clinical outcome, Medicaid Claims Data Study, and crizanlizumab/SUSTAIN study.



Sources: SUSTAIN Study, ⁴ VX21-SCD-002 CSR, ³ Brazauskas et al., ² Study 121/Table 14.2.1.1 (as of the data cutoff date of 14 June 2023)

exa-cel: exagamglogene autotemcel; HLA: human leukocyte antigen; PES: Primary Efficacy Set; VF12: absence of any severe VOCs for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crisis; Y: years

Notes: Response rates reflect VF12 in Study 121, 3-year event-free survival in the report by Brazauskas et al. ², and absence of VOC during the 12-month follow-up periods in the Medicaid claims data study VX21-SCD-002.

Source: BLA 125787/0/66, Clinical Information Amendment, p.2, Figure 1.

End of Reviewer Comment #5.

First key secondary efficacy endpoint: Proportion of HF12 responders

The first key secondary efficacy endpoint is the proportion of HF12 responders, patients free from inpatient hospitalization for sVOCs sustained for at least 12 months after exa-cel infusion. This endpoint has the same requirements as the VF12 responder endpoint, i.e., flexibility for the 12-month hospitalization period to occur anywhere within a 24-month F/U, start time of evaluation relative to last RBC transfusion, and requiring ≥ 16 months of F/U for evaluability.

The prohibited medication treatment period was excluded from the HF12 duration.

Biomarker endpoints: Hematologic parameters

- HbF as percentage of total Hb (HbF [%]) over time
- Levels of total Hb and HbF over time
- Measures of hemolysis

Biomarker endpoint: Allelic editing

- Proportion of alleles with intended genetic modifications in peripheral blood leukocytes and CD34+ cells of the bone marrow over time

Reviewer Comment #6: Review content

The Applicant planned for sequential testing for the primary and two key secondary efficacy endpoints. The 2nd key secondary efficacy endpoint is an intermediate clinical endpoint (proportion of VF9 responders) defined similar to the VF12 endpoint, with the 12-month sVOC-free duration replaced with a 9-month sVOC-free duration. This endpoint is intended solely to support the AA pathway. As we will not consider the AA pathway, this endpoint will not be reviewed. Additional endpoints that are prone to biases in a single-arm trial, and therefore are difficult to interpret and would not be included in labeling are not included in this memo. As described previously, other important endpoints are reviewed in detail by other review disciplines. I have included the Applicant's analyses on some biomarker endpoints for context on the mechanism of action.

End of Reviewer Comment #6.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Sets

- The **Enrolled Set** includes all enrolled subjects who have signed informed consent and met the eligibility criteria. Listing of the demographics and baseline characteristics will be provided based on the Enrolled Set.
- The **Safety Analysis Set (SAF)** is a subset of the Enrolled Set that includes subjects who have started the mobilization regimen.
- The **Full Analysis Set (FAS)** is a subset of the Enrolled Set that includes subjects who had received exa-cel infusion. The demographics and baseline characteristics will be summarized based on FAS.
- The **Primary Efficacy Set (PES)** is a subset of FAS that includes all subjects who have been followed for at least 16 months post exa-cel infusion and for at least 14 months after completion of the RBC transfusions for post-transplant

support or SCD management. **Completion of the (initial) RBC transfusions** is determined when all those transfusions for post-transplant support or SCD management have finished followed by 60 days without transfusion. **Subjects who complete the 24 months of follow-up in the study post exa-cel infusion will be included in this set.** In addition, subjects who die or discontinue the study due to **exa-cel-related adverse events** and have less than 16 months follow-up post exa-cel infusion, or continuously receive RBC transfusions for more than 10 months post exa-cel infusion will also be included in this set.

Sample size and interim analyses

The study planned to treat up to 17 subjects with possible expansion to a total of up to approximately 45 subjects. The study planned to perform 3 interim analyses (IAs, Table 6) when the study is expanded to treat up to approximately 45 subjects, following a group sequential testing procedure in the expanded study to allow for early evaluation of efficacy at interim sample sizes of 10, 17, and 30. The actual alpha spending will be based on the information available at the IA. This sample size and interim analysis plan will provide an overall power of at least 95% to rule out a null response rate of 50% or less for the primary efficacy endpoint (proportion of VF12 responders) if the true response rate is 80% with one-sided alpha of 2.5%.

Table 6. Study 121 interim analysis plan including efficacy boundary and alpha spending for the primary efficacy endpoint

Interim analysis #: sample size N	Efficacy Boundary: VF12 responder/N	One-sided alpha spent at a null response rate of 50%
IA1: N=10	9/10	0.01074
IA2: N=17	14/17	0.00366
IA3: N=30	22/30	0.00540
Final: N=45	31/45	0.00440
Overall		0.02420

Source: Adapted from - BLA 125787/0/8, Study 121 Statistical Analysis Plan Version 5.1 (US), Version Date December 08, 2022, Table 9-1, p.27.

Reviewer Comment #7: Interim analysis plan

Several issues, described below, with the Applicant's IA plan complicate interpretation of the treatment effect.

- The Applicant's final protocol (Version 6.11 dated September 15, 2022) and SAP (Version 5.1 dated December 08, 2022) reported different alpha spending. I have

replicated the numbers in the SAP and included them in Table 6 above. The numbers in the protocol appeared to be incorrect. This inconsistency may have reflected that the IAs were revised while the trial was ongoing and partial data had become available. As a result, it is difficult to be confident that the type 1 error rate is well-controlled. Of note, the IAs were initially planned when HbF level was proposed as the primary efficacy endpoint, and stayed the same when the endpoint was changed to VF12 response rate.

- During the BLA late-cycle review meeting, FDA advised the Applicant to report study results at IA3 with the corresponding allotted alpha as given in Table 6, i.e., 0.00540. The Applicant stated that IA1 was never performed and IA3 was performed per FDA's request, and therefore alpha from IA1 and IA2 should be recovered. The Applicant proposed that, for IA3, the cumulative one-sided alpha should be the sum of the alpha allotted to the three IAs, i.e., 0.01980 ($=0.01074 + 0.00366 + 0.00540$). It is not clear how best to control the type 1 error rate given the lack of full pre-specification of the IA plan and the deviation of the conducted IAs from the plan. Nevertheless, the FDA agrees with the Applicant's request to use a one-sided alpha level of 0.01980 to report results for IA3, given that it is the analysis FDA focuses on. In addition, given that the null hypothesis response rate of 50% was not well-supported (see discussion under **Reviewer Comment #5**), it is questionable to report statistical significance in testing against this null hypothesis. As a result, we recommend the Applicant to report one-sided CI on the primary efficacy endpoint with a confidence level of 0.98 ($\approx 1 - 0.01980$), instead of reporting p-values of tests against a null of 50%.
- During the same late-cycle review meeting, the Applicant requested to use two-sided 95% confidence levels to report CIs, regardless of statistical significance levels used for the corresponding statistical tests. FDA disagrees with this proposal and recommends reporting CIs with confidence levels consistent with the significance levels of the corresponding statistical tests. Our recommendation aligns with general practice and two guidance documents: (1) ICH E9 Statistical Principles for Clinical Trials (1998) Section 5.6 and (2) Adaptive Designs for Clinical Trials of Drugs and Biologics (2019) Section V.A. In particular, we quote the latter guidance *"To ensure the scientific and statistical credibility of trial results and facilitate important benefit-risk considerations, an approach for calculating estimates and confidence intervals that appropriately accounts for the group sequential design should be prospectively planned and used for reporting results."*

End of Reviewer Comment #7.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Table 7 summarizes the demographics of Study 121 subjects at IA3. The FAS and PES are generally comparable, except for age categories, where FAS has 27% (n=12) adolescents compared to 20% (n=6) adolescents in the PES. The majority of treated patients (87%) in PES are Black or African American. There is roughly equal numbers of males and females. The median age at screening was 21 years with a range of 12 to 34 years. The first subject signed the informed consent form on November 27, 2018.

Table 7. Demographics in Study 121 subjects at interim analysis 3.

Demographics	Primary Efficacy Set (N=30)	Full Analysis Set (N=44)
Sex, n (%)		
Male	16 (53)	24 (55)
Female	14 (47)	20 (45)
Childbearing potential among females, n (%)		
Yes	14 (100)	20 (100)
No	0	0
Age at screening (years)		
Median	21	20
(Min, Max)	12, 34	12, 34
Age category at screening, n (%)		
≥12 and <18 years	6 (20)	12 (27)
≥18 and ≤35 years	24 (80)	32 (73)
Race, n (%)		
White	1 (3.3)	3 (6.8)
Black or African American	26 (86.7)	38 (86.4)
Asian	0	0
American Indian or Alaska Native	0	0

Native Hawaiian or other Pacific Islander	0	0
Not collected per local regulations	0	0
Other	3 (10.0)	3 (6.8)
Multiracial	0	0
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)

Source: Adapted from - Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Table 3, p.13.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 8 summarizes the baseline characteristics of Study 121 subjects at IA3.

The FAS and PES are generally comparable, with wider range for some characteristics in FAS, potentially due to its larger sample size. In what follows, I will describe the baseline characteristics in the PES. The majority of subjects (97%) has the β^S/β^S genotype. The median annualized rate of sVOCs at baseline was 3.3 events/year with a range of 2.0 to 9.5. The median annualized units of RBCs transfused for SCD-related indications was 3.3 with a range of 0.0 to 75.5.

Table 8. Baseline Characteristics in Study 121 subjects at interim analysis 3.

Baseline Characteristics	Primary Efficacy Set (N=30)	Full Analysis Set (N=44)
Genotype, n (%)		
β^S/β^S	29 (97)	40 (91)
β^S/β^0	1 (3)	3 (7)
β^S/β^+	0	1 (2)
HbF (g/dL)		
n	29	43
Median	0.4	0.4
(Min, Max)	(0.0, 1.5)	(0.0, 1.5)
HbF (%)		
n	30	44

Median	5.3	5.0
(Min, Max)	(0.0, 14.7)	(0.0, 14.7)
Total Hb (g/dL)		
n	29	43
Median	9.4	9.4
(Min, Max)	(5.7, 12.6)	(5.7, 12.6)
Annualized rate of severe VOCs		
n	30	44
Median	3.3	3.5
(Min, Max)	(2.0, 9.5)	(2.0, 18.5)
Annualized rate of inpatient hospitalizations for severe VOCs		
Median	2.0	2.5
(Min, Max)	(0.5, 8.5)	(0.5, 9.5)
Annualized duration of inpatient hospitalizations for severe VOCs (days)		
Median	12.3	14.0
(Min, Max)	(2.0, 64.6)	(2.0, 136.5)
Annualized units of RBCs transfused for SCD-related indications		
Median	3.3	5.0
(Min, Max)	(0.0, 75.5)	(0.0, 86.1)
Weight (kg)		
Median	65.5	67.0
(Min, Max)	(43.0, 95.0)	(34.0, 116.0)

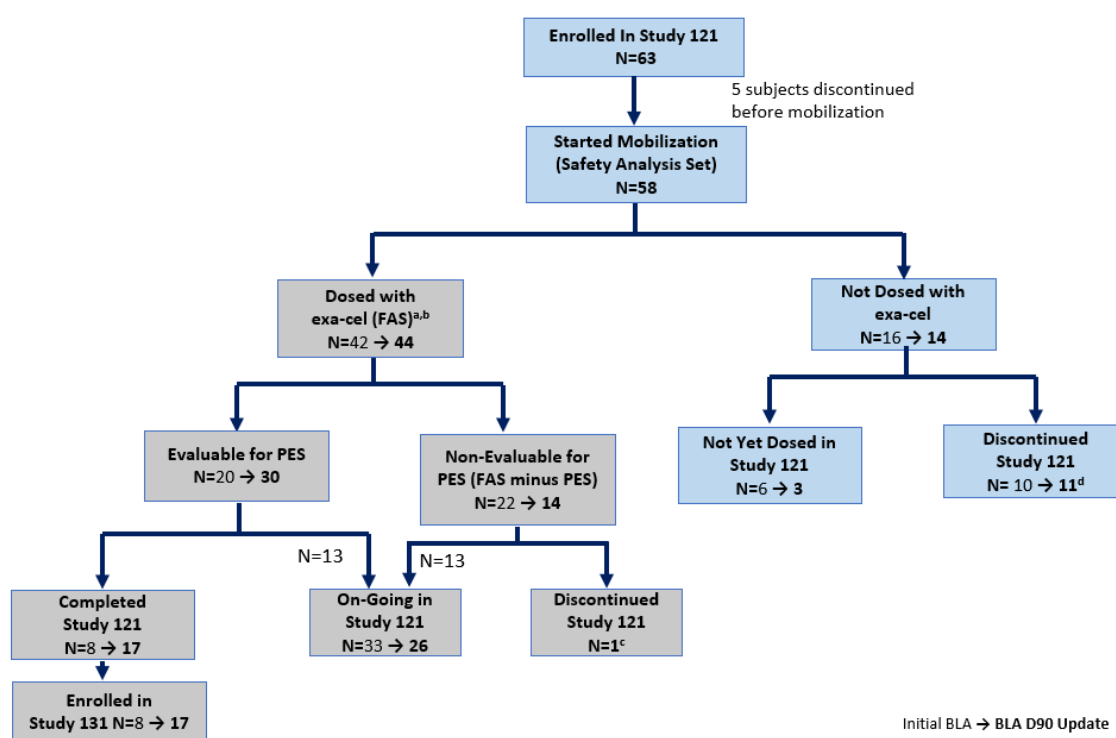
Source: Adapted from - Original BLA 125787/0/36, EXA-CEL SCD CLINICAL
ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Table 4, pp.14-15.

6.1.10.1.3 Subject Disposition

Figure 4 summarizes SCD subject disposition in Studies 121 and 131, at IA2 and IA3. In what follows, I will only summarize the disposition at IA3. A total of 63 subjects signed informed consent and met the eligibility criteria, of which 58 (92%) started mobilization and constituted the Safety Analysis Set. Among the subjects who started mobilization, 11

subjects (11/58, 19%) discontinued after mobilization without receiving exa-cel, and another 3 subjects (3/58, 5%) had not yet received exa-cel at IA3. The remaining 44 subjects (76%) received exa-cel and forms the FAS, of which 30 had at least 16 months of F/U after exa-cel infusion and forms the PES. Of the PES, 17 had completed the two-year F/U in Study 121 and enrolled in Study 131 for LTFU, and another 13 subjects, together with 14 FAS subjects not in PES, are ongoing in Study 121. One treated subject in the FAS died on Month 8.9. Table 9 provides more details on F/U. Note that in Table 9, months was calculated as days divided by 30 following the Applicant's approach, though a more accurate approach would be division by 30.4.

Figure 4. Subject disposition for all enrolled subjects in Study 121 and all SCD subjects in Study 131 at interim analyses #2 and #3.



Source: BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Figure 1, p.11 of 90.

Table 9. Follow-up duration from exa-cel infusion to data cutoff date of interim analysis 3 in Studies 121 and 131 (FAS, N=44).

Parameters	Summary
Follow-up duration in months	
Median	19.3
(Minimum, Maximum)	(0.8, 48.1)

Total follow-up duration in patient-months	882.4
Total follow-up duration in patient-years	73.5
Follow-up duration by interval, n (%)	
≤3 months	1 (2.3)
>3 months to ≤6 months	2 (4.5)
>6 months to ≤12 months	8 (18.2)
>12 months to ≤24 months	16 (36.4)
>24 months	17 (38.6)

Source: Adapted from - Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Table 14, p.50.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Figure 5 displays the sVOCs during the 2-year baseline period and the period after exa-cel infusion for all 44 FAS subjects at the time of IA3. In the FAS (N=44), at baseline 75% of the subjects had ≤ 4.0 sVOCs/year, with a range of 2.0 to 18.5 sVOCs/year. In the PES (N=30), at baseline 77% of the subjects had ≤ 4.5 sVOCs/year, with a range of 2.0 to 9.5 sVOCs/year.

Reviewer Comment #8: Baseline sVOC

The Applicant stated that Study 121 required subjects to have ≥2 sVOCs for each of the two years prior to trial enrollment. However, I identified multiple instances where, in subjects with low baseline sVOCs (≤ 3 sVOCs/year), some sVOCs occurred much closer in time than expected, raising questions whether those sVOCs reported as separate occurrences should have been counted as a single occurrence, and as a consequence might have disqualified some PES and FAS subjects. It also raised questions that having EAC adjudication alone might not have guarded adequately against potential biases in this single-arm trial. I discussed this issue with the clinical reviewer, and learned that adjudicating sVOCs can be difficult, and the results may depend on the specific process, e.g., whether the EAC members knew the sVOCs were from the same subject or were adjudicating each potential sVOC without knowledge of other potential sVOCs submitted for adjudication for the same subject. Given the challenges with unambiguous counting of sVOCs at baseline, we do not present the effect of exa-cel as a numerical reduction in sVOCs rates.

Of the 44 FAS subjects, 21 (48%) had ≤ 3 sVOCs/year during the baseline period of 2 years or longer. Table 10 lists the sVOCs that are separated by ≤20 days. A total of 8

subjects (8/21, 38%) had at least a pair of sVOCs separated by ≤ 20 days. For example, Subject (b) (6) experienced a total of 4 EAC-adjudicated baseline sVOCs during the 2-year baseline period; the first two sVOCs were separated by 6 days while the last two were separated by 2 days. If any of the two pairs should be counted as just one sVOC occurrence, this subject would not have met the eligibility criteria. There are several instances of successive sVOCs being separated by no more than one day, e.g., (b) (6) and (b) (6). While I did not attempt to examine the pattern in subjects with >3 sVOCs/year at baseline as it would be more difficult to delineate whether the pattern can be due to chance alone, there is no reason to expect that the potential overcounting we observe in the baseline ≤ 3 sVOCs/year group would not be present in the baseline >3 sVOCs/year group. The consequence is potential inclusion of ineligible subjects and overestimation of baseline severity.

Note that the Study Days in the Table were counted from the exa-cel infusion day while the two years in baseline were counted from the enrollment day. Some of the baseline Study Day are substantially more than 2 years counting back from the exa-cel infusion day because there were substantial times elapsed from enrollment day to infusion day.

Table 10. Baseline sVOCs separated by less than 20 days in subjects with ≤ 3 sVOCs/year during baseline (N=21).

Subject ID	In PES?	Baseline: # sVOCs/year	sVOC start and end time in Study Days from exa-cel infusion (each occurrence on a separate line)
(b) (6)	N	3.0	-864 to -864 -853 to -840 [Packet incomplete but adequate for adjudication]
(b) (6)	Y	2.0	-623 to -623 -619 to -619 [Packet inadequate for adjudication (specify missing data in Comments)]
(b) (6)	N	2.5	-1350 -1349 to -1348
(b) (6)	Y	2.0	-714 to -714 -708 to -705 [Packet incomplete but adequate for adjudication] -459 to -455 -453 to -448
(b) (6)	Y	3.0	-962 to -962 [Packet incomplete but adequate for adjudication] -956 to -949 [Packet incomplete but adequate for adjudication]

(b) (6)	Y	2.5	-587 to -586 -586 to -585
(b) (6)	Y	2.5	-844 to -844 -824 to -824 -802 to -791 [Note this is 22 days from last one]
(b) (6)	N	2.5	-978 to -972 [Packet incomplete but adequate for adjudication] -966 to -946

Abbreviation: sVOCs, severe vaso-occlusive crisis; PES, Primary Efficacy Set.

Note: All the sVOCs in this Table are “acute pain”.

Source: Reviewer’s Analysis.

End of Reviewer Comment #8.

The Applicant reported that there were 30 subjects in the PES, i.e., those that had at least 16 months of F/U after exa-cel infusion, and only one of them did not achieve VF12 response. Therefore, the Applicant reported the VF12 response rate in the PES as 29/30 (96.7%), together with a 95% CI and a p-value for testing against a null response rate of 50%.

Reviewer Comment #9: Primary analysis of primary endpoint

I disagreed with the Applicant’s analysis. After internal discussion and interaction with the Applicant, **FDA recommended reporting the primary analysis on VF12 response rate as 29/31 (93.5%) with a one-sided 98% CI of (77.9%, 100%) without reporting any p-values. Below is a summary of the considerations.**

1. As described under **Reviewer Comment #7**, a one-sided 98% confidence level should be used to match the one-sided type 1 error rate of 0.0198 allotted to IA3. We used 0.02 instead of 0.0198 for ease of communication, and because there is no material difference between the two confidence levels. We advised against performing a statistical test with a null response rate of 50%, given that we are not confident 50% is an adequate null response rate as described under **Reviewer Comment #5**. However, we believe a lower bound of 77.9% does exclude a response rate due to chance alone, barring undetected serious biases, and therefore provides substantial evidence for the effectiveness of exa-cel.
2. The Applicant excluded Subject # (b) (6), who had 14.3 months of F/U by IA3 data cutoff date, from the PES, which required 16 months of F/U per Applicant’s definition. As discussed under **Reviewer Comment #4**, this is not a reasonable requirement for membership in PES, as it is neither sufficient nor necessary to determine VF12 response status in some situations. Subject #^{(b) (6)}, the subject right below the orange line in Figure 5, experienced three

sVOCs at Months 11.7, 12.8, and 14.1, and therefore is a VF12 non-responder. We recommended to include this subject as a VF12 non-responder in the VF12 response rate estimation. Therefore, the primary analysis of the primary efficacy endpoint would report an estimate of the response rate being 29/31. As the Applicant had referred to PES as the set of 30 subjects without Subject # (b) (6) in various analysis, to avoid complication we will refer to PES as the same set of 30 subject, unless otherwise noted.

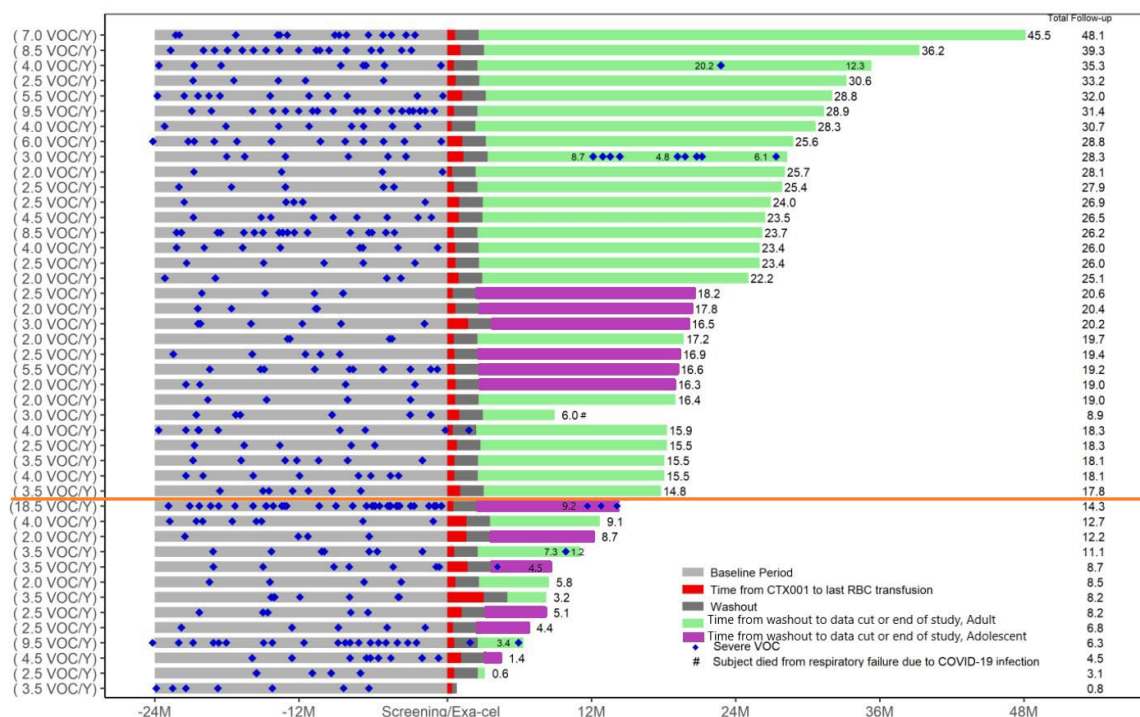
3. The Applicant excluded Subject # (b) (6), who died on Month 8.9, from the PES. I initially recommended including this subject as a VF12 non-responder in the PES, given that the investigator determined that the death was related to COVID-19 and busulfan, and busulfan is an integral component of the exa-cel treatment regimen. Upon further discussion with the clinical review team, I agreed to the Applicant's initial approach of excluding this subject from the PES, given that it was difficult to delineate the extent of busulfan's contribution to the death among the comorbidities. As a sensitivity analysis, counting this subject as a non-responder in the PES would yield an estimate of the response rate as 29/32 (90.6%, 98% one-sided CI: [74.2%, 100%]). This sensitivity analysis does not change my conclusion that exa-cel is effective.
4. Of the two VF12 non-responders, Subject (b) (6) experienced 9 acute pain episodes with emergency room visits from Day 364 to Day 821 (Month 12.1 to 27.4), and Subject (b) (6) experienced 3 acute pain episodes with emergency room visits from Day 350 to Day 424 (Month 11.7 to 14.1). A VF12 responder, Subject (b) (6), experienced an acute pain episode that required a 5-day hospitalization starting Day 639 (Month 30.0). Three other FAS subjects, whose VF12 response status could not yet be determined, experienced sVOCs after exa-cel infusion.
 - a. Subject (b) (6), aged 24, had an acute pain episode with a 2-day hospitalization starting Day 297 (Month 9.9)
 - b. Subject (b) (6), aged 17, had an acute pain episode with an outpatient clinic visit on Day 126 (Month 4.2)
 - c. Subject (b) (6), aged 19, had 2 acute pain episodes with a one-day hospitalization each on Days 70 and 186 (Months 2.3 and 6.2)

Interpretation of treatment effect size. As previously described, the combination of multiple flexibilities in the definition of VF12 response has complicated the interpretation of the treatment effect size, in part by making it difficult to estimate a reasonable null response rate to which the VF12 response rate after exa-cel treatment should be compared. It is reassuring that Figure 5 shows that, the estimated VF12 response rate after exa-cel treatment would not change if a fixed-period (e.g., from Month 7 to 18, inclusive) definition is used instead. This indicates, indeed, the treatment effect of exa-cel may be substantial. However, it is not appropriate to change the endpoint post-hoc. In

addition, it is unknown at this time whether the fixed-period vs. flexible-period definitions would lead to appreciably different results at the final analysis, when all treated subjects have been followed up for 24 months. As described in item 4 above, 2 of the remaining 12 subjects with yet-undetermined VF12 response status would have been a non-responder for a fixed-period response endpoint with a Months 7 to 18 (inclusive) response period.

End of Reviewer Comment #9.

Figure 5. Severe VOCs during baseline and after exa-cel infusion in Studies 121 and 131 at interim analysis #3 (Full Analysis Set, N=44)



Notes: The Figure displays only severe VOCs submitted by investigators to the Endpoint Adjudication Committee (EAC) that were adjudicated by the EAC as meeting the protocol criteria.

Baseline period was the 2 years prior to most recent screening. The number on the right end is the duration of total follow-up in months. (# VOC/Y) on the left end is the baseline annualized rate of severe VOCs.

Orange line demarcates the subjects (i.e., those above the line) that were included in the primary efficacy set (PES) with at least 16 months of follow up.

The cause of the death is over-simplified in the figure. Please refer to Section “6.1.12.3 Deaths” in this memo for more information.

The period from enrollment to exa-cel infusion was excluded from the Figure.

Abbreviations: CTX001, exa-cel; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis; Y, year.

Source: Adapted from - FDA's briefing document for advisory committee meeting, p.22, Figure 9, which was further adapted from BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, p.19, Figure 2.

6.1.11.2 Analyses of Secondary Endpoints

As previously described, I will only review HF12, the first key secondary endpoint. All 30 subjects in the PES are HF12 responders, i.e., free from inpatient hospitalization due to EAC-adjudicated sVOCs for at least 12 months after exa-cel infusion. This yields a response rate of 100% with a 98% one-sided CI of (87.8%, 100%). Note that although Subject # (b) (6) was included in the PES, it is not yet possible to determine whether this subject will be a HF12 responder.

6.1.11.3 Subpopulation Analyses

There are roughly equal numbers of males and females in the primary efficacy analysis, and there was one male and one female VF12 non-responder. Therefore, the treatment effect is consistent in males and females.

For all other baseline characteristics of interest, the subgroups formed by each characteristic were unbalanced, leaving one subgroup with very few subjects. This precludes meaningful evaluation of the consistency of treatment effect in subgroups formed by that characteristic. For example, 29 of the 30 subjects in PES had β^S/β^S while only one subject had β^S/β^0 .

In what follows I will examine two factors, age and clinical site, which show patterns warranting further discussion.

Subgroup analysis by age

The 6 adolescents in the PES had F/U of 19.0 to 20.6 months after exa-cel infusion, compared to a range of 17.8 to 48.1 months of F/U in 24 adults. This is probably due to the study design, with adolescents starting exa-cel only after initial data from adults became available and it was determined to warrant expanding treatment to adolescents.

Subgroup analysis by clinical site

A total of 7 and 10 clinical sites contribute data to the PES and FAS, respectively (Table 11). Site 006 dominates, contributing 50% and 39% of the subjects in PES and FAS, respectively, while each of the other sites contribute $\leq 13\%$ of the subjects in PES. It also appears that Site 006 had comparatively more favorable results (Table 12). In PES, Site 006 had longer total F/U (400 months) than all the other sites combined (368 months), but none of the Site 006 subjects experienced any sVOCs, while 3 subjects in the other sites experienced 11 sVOCs. It is unclear whether chance alone or some other site-specific characteristics contribute to this difference between Site 006 and other sites.

In addition, several subjects transferred from Site 001 (San Antonio, Texas) to Site 006 (Nashville, Tennessee). Of the 5 subjects enrolled at Site 001, one completed Study 121 and transferred to Site 115 for LTFU in Study 131, another one requested and was dosed at Site 006 but was later transferred back to Site 001 due to a serious adverse event (SAE) and subsequently died. A third subject requested and was dosed and followed-up at Site 006. The remaining two subjects enrolled at Site 001 later and were dosed at Site 001, and they were then transferred for F/U to Site 006 due to the departure of the principal investigator and site closure. It appeared that, for the three subjects who enrolled at Site 001 but transferred to Site 006 for exa-cel treatment and/or F/U, some information was collected remotely. It is not clear how this would impact data quality.

Table 11. Study 121: Exa-cel treated subjects by clinical site

Site	Full Analysis Set (N=44) Number of Subject (%)	Primary Efficacy Set (N=30) Number of Subject (%)
006	17 (39%)	15 (50%)
103	6 (14%)	3 (10%)
007	5 (11%)	2 (7%)
009	4 (9%)	4 (13%)
005	3 (7%)	3 (10%)
001	2 (5%)	1 (3%)
003	2 (5%)	
004	2 (5%)	2 (7%)
014	2 (5%)	
105	1 (2%)	

Source: Reviewer's analysis.

Table 12. Total follow-up duration and number of sVOCs: Site 006 versus all other sites

Parameter: Total follow-up or sVOC	Site 006	All Other Sites Combined
PES (N=30): Total follow-up (months) [# subjects]	400 [15]	368 [15]
PES (N=30): # sVOCs [# subjects with ≥ 1 sVOCs]	0 [0]	11 [3]
FAS (N=44): Total follow-up (months) [# subjects]	413 [17]	469 [27]
FAS (N=44): # sVOCs [# subjects with ≥ 1 sVOCs]	0 [0]	18 [7]

Abbreviations: PES, Primary Efficacy Set; FAS: Full Analysis Set; sVOC, severe vaso-occlusive crisis.

Source: Reviewer's analysis.

6.1.11.4 Dropouts and/or Discontinuations

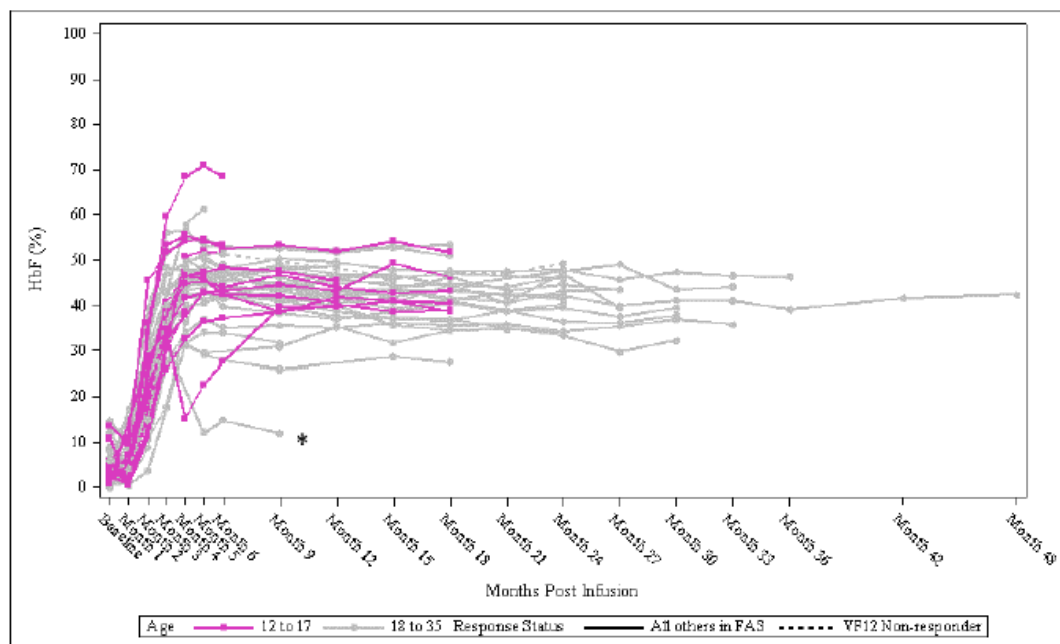
There is no dropouts or discontinuations in Study 121. One death occurred. See Section "6.1.12.3 Deaths" for more information.

6.1.11.5 Exploratory and Post Hoc Analyses

Hematologic parameters and allelic editing

Figures 6 to 9 are the Applicant's presentation of subject-level time course of HbF (%), F-cells (%), alleles with intended genetic modifications present in CD34+ cells of the bone marrow, and that present in peripheral blood leukocytes, respectively. In the same document, the Applicant reported Total Hb and HbF only as means across individual, which does not capture inter-subject variability and are therefore not included in this memo. The reported parameters all increase appreciably and stay stable during the F/U period. Please refer to the memo by the clinical pharmacology reviewer for details.

Figure 6. Subject-level HbF (%) time course (Full Analysis Set, N=44)



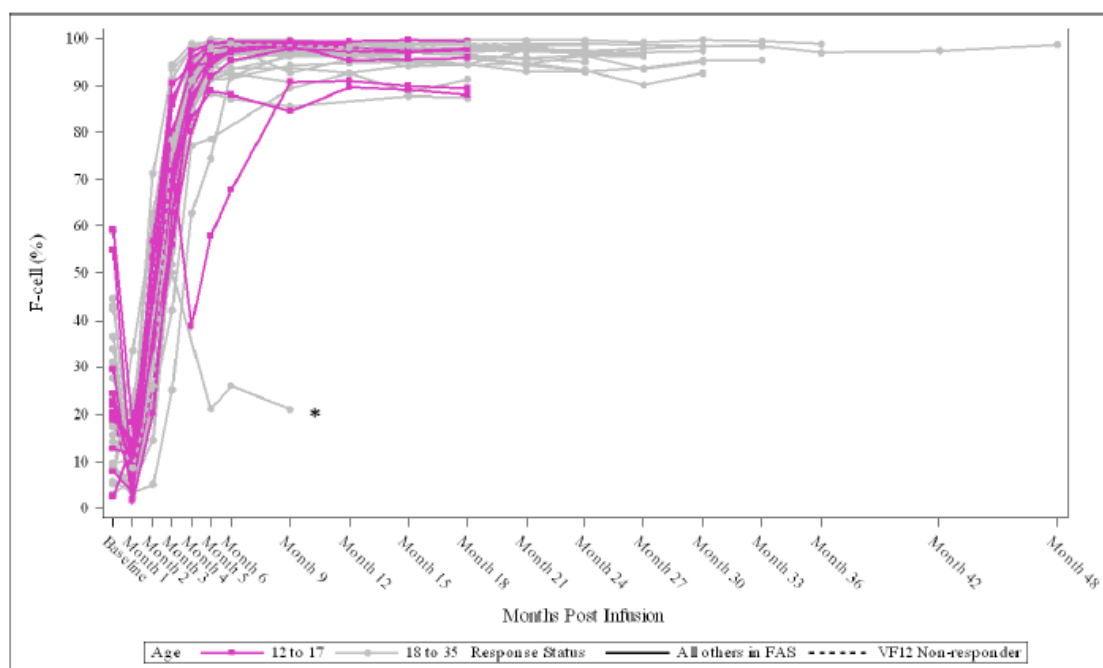
Source: [Study 131/figure 14.2.4.3b](#) (data cutoff date of 14 June 2023)

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: * indicates Subject (b) (6) who died due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel. This subject 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. One subject (Subject (b) (6) shown 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 (scheduled or unscheduled) collected before the start of mobilization in Study 121. Analysis visit was used in the figure.

Source: Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Figure 11, p.40.

Figure 7. Subject-level F-cell (%) time course (Full Analysis Set, N=44)



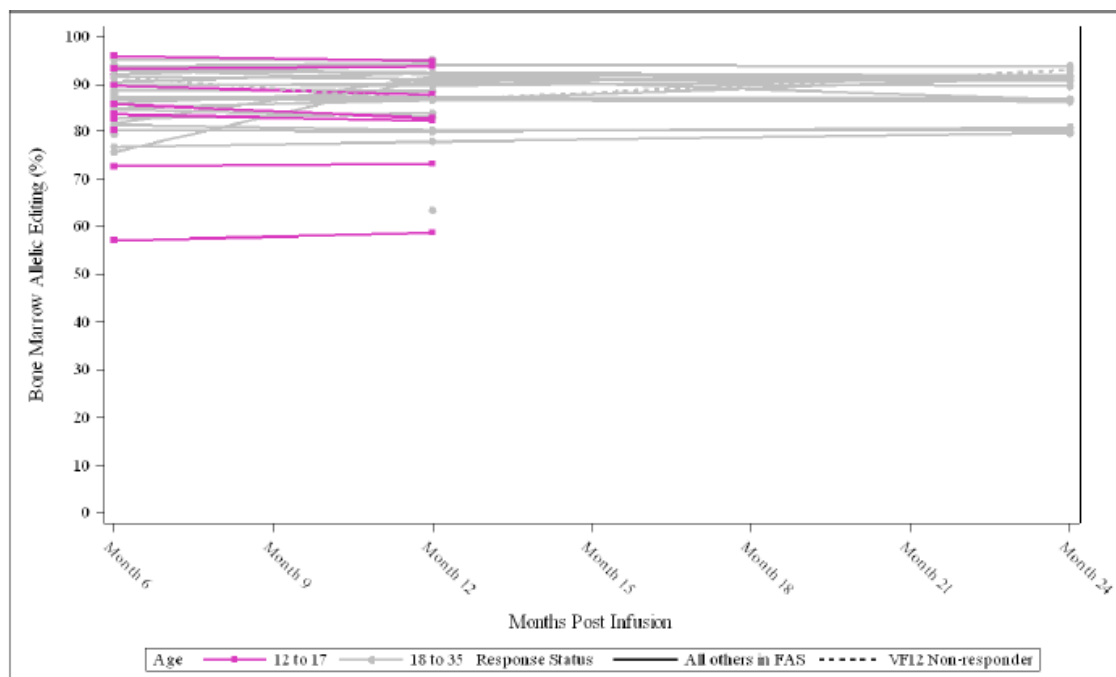
Source: Study 131/Ad hoc Figure 14.2.11.3b (data cutoff date of 14 June 2023)

F-cells: circulating RBCs expressing detectable levels of HbF; FAS: Full Analysis Set; HbF: fetal hemoglobin; 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

Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure. *indicates Subject (b) (6) who died due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.

Source: Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM:
EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Figure 12, p.41.

Figure 8. Subject-level time course of proportion (%) of alleles with intended genetic modification present in CD34+ cells of the bone marrow (Full Analysis Set, N=44)



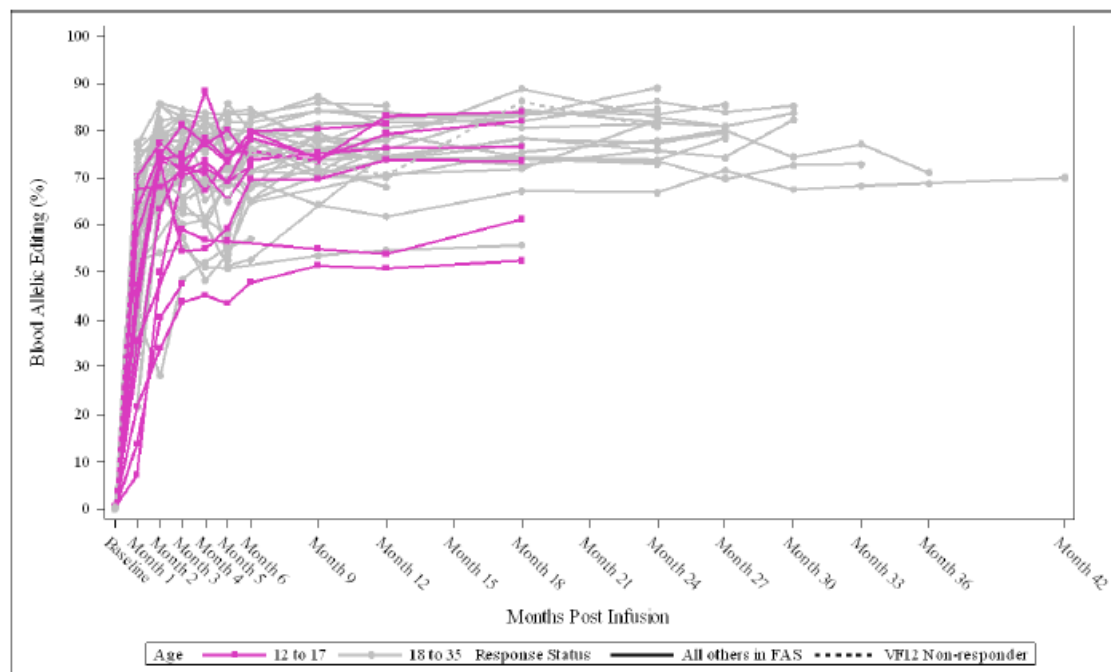
Source: Study 131/Ad hoc Figure 14.2.9.3b (data cutoff date of 14 June 2023)

FAS: Full Analysis 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

Note: Analysis visit was used in the figure. One subject (represented by gray dot) had bone marrow allelic editing data at Month 12 but not at Month 6.

Source: Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM:
EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Figure 13, p.42.

Figure 9. Subject-level time course of proportion (%) of alleles with intended genetic modification present in peripheral blood leukocytes (Full Analysis Set, N=44)



Source: Study 131/Ad hoc Figure 14.2.7.3b (data cutoff date of 14 June 2023)

FAS: Full Analysis 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

Note: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

Source: Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Figure 14, p.43.

Hemolysis measures

The Applicant made statements regarding lactate dehydrogenase (LDH) and haptoglobin, measures of intravascular hemolysis, the dominant mechanism of hemolysis in SCD: “Mean LDH levels normalized by Month 9 and all patients with follow-up data generally had detectable and durable haptoglobin levels after Month 6.” (Advisory committee meeting Applicant briefing document, p.20). These statements appear vague to me without supporting analyses reported. Therefore, it is unclear that their conclusion “these results indicate that exa-cel confers broad protection of RBCs and the resolution of hemolysis” is supported by evidence. I defer the review of these statements to other review disciplines with subject matter expertise.

6.1.12 Safety Analyses

There are theoretical safety concerns related to the MOA of exa-cel. The following is excerpted from the reference “Katie Kingwell (2023) First CRISPR therapy seeks landmark approval. *Nature Reviews Drug Discovery* 22, 339-341 doi: <https://doi.org/10.1038/d41573-023-00050-8>”:

To achieve gene silencing, the Cas nuclease makes double-stranded DNA breaks that are then mis-repaired by the cell. However, this can lead to large genomic rearrangements and translocations in vitro, as well as complete loss of the target chromosome through a process called chromothripsis. These effects have not been reported in treated patients so far, and could well cause affected cells to die before they are even re-infused into patients. ... But these editing events still raise the spectre of oncogenic and other serious risks.

Another potential risk stems from the possibility that the editor's guide RNA can direct the Cas nuclease to cut similar, non-target, sites — resulting in off-target editing. Researchers have made good inroads in predicting and mitigating these liabilities, however, through deep sequencing to screen for genomic sites that might match the guide RNA, and by selecting Cas nucleases with more stringent editing windows, ...

It is likely not feasible to assess these theoretical safety concerns empirically in pre-marketing clinical trials, which generally have a limited number and F/U of treated patients. The Applicant has proposed a 15-year LTFU study (Study 131) for patients who received exa-cel in their clinical trials and a 15-year registry-based prospective observational study for patients who will receive commercial exa-cel.

6.1.12.3 Deaths

One death occurred in Study 121, to a 33-year-old Black female participant on Day 268 (Month 8.9). The investigator determined that the death was not related to exa-cel, but rather was related to COVID-19 and busulfan. Lung injury and serious infections, including fatal outcomes, are known risks of busulfan treatment. However, note that busulfan is an integral component of the exa-cel treatment regimen. Please refer to the clinical review memo for details.

6.1.12.4 Nonfatal Serious Adverse Events

Table 13 summarizes serious adverse events (SAEs) occurring in ≥ 2 patients in the 44 subjects who received exa-cel for the two-year period after exa-cel infusion in Study 121. Twenty (45.5%) subjects experienced at least one SAE during this period. Table 14 summarizes SAEs occurring in ≥ 2 patients in the 58 subjects who started mobilization, for the period from mobilization to prior to conditioning. Thirty-five (60.3%) subjects experienced at least one SAE during this period.

Table 13. Serious adverse events occurring in ≥ 2 patients from exa-cel infusion through 2 years of follow-up (Study 121, FAS, N=44)

Preferred Term	n (%)
Patients with any serious adverse event	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)
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)

Source: Adapted from - Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Table 21, p.61.

Table 14. Serious adverse events occurring in > 1 patients during the period from mobilization to prior to conditioning (Study 121, Safety Analysis Set, N=58)

Preferred Term	n (%)
Patients with any serious adverse event	35 (60.3)
Sickle cell anemia with crisis	20 (34.5)
Abdominal pain	4 (6.9)
Acute chest syndrome	3 (5.2)
Back pain	3 (5.2)
Vascular device infection	3 (5.2)
Anxiety	2 (3.4)
Bacteremia	2 (3.4)
Bone pain	2 (3.4)
Pulmonary embolism	2 (3.4)
Staphylococcal bacteremia	2 (3.4)

Source: Adapted from - Original BLA 125787/0/36, EXA-CEL SCD CLINICAL ADDENDUM: EFFICACY AND SAFETY UPDATE 14 JUNE 2023, Table 26, p.70.

Reviewer Comment #10: Applicant's safety conclusion

The Applicant concluded that *"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."* It should be noted that at this time busulfan conditioning is an integral component of the exa-cel treatment regimen.

Therefore, when assessing the benefit-risk profile of exa-cel, the risk associated with the entire treatment regimen, including busulfan conditioning, should be considered.

End of Reviewer Comment #10.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The data package reviewed in this memo was based on the 3rd IA with an allotted one-sided type 1 error rate of 0.02 for analyses based on PES.

There are several issues with the definition of the VF12 response. It is different from a more natural definition for user interpretation where efficacy evaluation would start from the time when the therapy starts taking effect, e.g., Months 7 to 18, inclusive, after investigational product administration. There are multiple types of flexibility in the definition of the protocol-defined VF12 response, e.g., the 12-month sVOC-free period can be achieved anywhere within the 24-month F/U period. This flexibility in the evaluation period alone would lead to at least a 2-3 folds increase in the chance of observing a response when there is no treatment effect, compared to a fixed-period (e.g., Months 7 to 18) response endpoint. I find the Applicant's rationales for the choice of a 50% VF12 null response rate inadequate by failing to address the flexibilities in the VF12 response definition, even though they acknowledged that these would affect the null. Therefore, I do not recommend reporting study results on VF12 in terms of a p-value testing the VF12 response rate against a null rate of 50%.

Efficacy results

In the PES (N=30), at baseline 77% of the subjects had ≤ 4.5 sVOCs/year, with a range of 2.0 to 9.5 sVOCs/year. There are roughly equal numbers of males and females. The primary analysis of the primary efficacy endpoint, VF12 response rate, was a point estimate of 93.5% (29/31) with a one-sided 98% confidence interval (CI) of (77.9%, 100%). The Applicant proposed to include only those subjects with at least 16 months of F/U after exa-cel infusion in PES. However, an additional non-PES subject, with 14.3 months of F/U and three sVOCs at Months 11.7, 12.8, and 14.1, was clearly a VF12 non-responder and is therefore included in the estimate of the VF12 response rate.

A death occurred on Day 268 (Month 8.9). I proposed to include this death as a VF12 non-responder, as it was reported by the investigator to be related to COVID-19 and busulfan, the latter being an integral component of the exa-cel treatment regimen. I

ultimately agreed with the FDA clinical team's decision to exclude this subject from the efficacy analysis as it is challenging to delineate the role of busulfan in the death among the multiple comorbidities.

Of the two VF12 non-responders, Subject (b) (6) experienced 9 acute pain episodes with emergency room visits from Day 364 to Day 821 (Months 12.1 to 27.4), and Subject (b) (6) experienced 3 acute pain episodes with emergency room visits from Day 350 to Day 424 (Month 11.7 to 14.1). A VF12 responder, Subject (b) (6), experienced an acute pain episode that required a 5-day hospitalization starting Day 639 (Month 30.0) after initially achieving VF12 response.

Of the remaining 12 subjects whose VF12 response status could not yet be determined at IA3 and therefore were not included in the primary efficacy analysis, 3 subjects experienced acute pain episodes determined to meet the sVOC definition. In two of these subjects, the sVOCs were associated with hospitalizations: one subject had 1 sVOCs at Month 9.9 and the other had 2 sVOCs at Months 2.3 and 6.2, respectively. The third subject had an acute pain episode with an outpatient clinic visit on Month 4.2.

Several issues complicate the interpretation of the magnitude of and the assessment of the robustness of exa-cel's treatment effect in terms of VF12 response rate, the primary efficacy endpoint.

- Contrary to a more natural response definition with response evaluation starting at a fixed time point when exa-cel were expected to take effect, e.g., Month 7, Study 121 defined VF12 response status with multiple types of flexibilities, some of which were introduced while study data had become available. One such flexibility was that any 12-month sVOC-free period during the 24-month F/U period would qualify as a VF12 response. This flexibility alone would increase the null response rate to at least 2-3 folds of the null response rate for a fixed-period response definition. The 50% response rate chosen by the Applicant therefore was not well supported by the Applicant's rationales, which did not consider the effect of any of the flexibilities. The unique VF12 response definition in Study 121 makes it difficult to identify a null response rate against which to compare the exa-cel response rate.
- VF12 response determination included only sVOCs adjudicated by the EAC, and only potential sVOCs reported by the investigator received EAC adjudication. In addition, there appears to be a lack of a standardized and structured approach to ensure all VOCs were recorded by the study subjects and were reported to the investigators. Whether this process introduced biases, and the extent of biases in the single-arm study, are unknown.
- There appears to be potential over-counting of baseline sVOCs, indicated by the observation that 8 of the 21 subjects reported to have ≤ 3 sVOCs/year during baseline had at least two sVOCs separated by 20 days or less.

- One clinical site contributed around 50% of efficacy data for the IA, with an indication of better results at this site compared to other sites on average.
- The limited sample size (N=31) and F/U at the IA limited assessment of the robustness of the treatment effect across subgroups defined by various factors. For example, only 7 adolescents were evaluable for VF12 response, and only one subject had the β^S/β^0 genotype.
- The Applicant revised the protocol and the statistical analysis plan (SAP) substantially while Study 121 was ongoing, with the final SAP containing some revisions submitted only at the time of the BLA submission. The FDA review team did not agree with all of these revisions.

Despite the limitations of the efficacy results, I conclude that the overall study result indicates that exa-cel is effective during the F/U. This conclusion is based in part on consultation with the clinical review team, and supported by the clear mechanism of action and the stable expression of HbF during the F/U period.

Safety results

One death occurred in Study 121, to a 33-year-old Black female participant on Day 268 (Month 8.9). The investigator determined that the death was not related to exa-cel, but rather was related to COVID-19 and busulfan. However, busulfan is an integral component of the exa-cel treatment regimen.

The Applicant concluded that “*The safety profile of exa-cel was generally consistent with that expected from myeloablative busulfan conditioning and [hematopoietic stem cell transplantation] HSCT, with delayed platelet engraftment the only exa-cel specific risk identified.*” It should be noted that at this time busulfan conditioning is an integral component of the exa-cel treatment regimen. Therefore, when assessing the benefit-risk profile of exa-cel, the risk associated with the entire treatment regimen, including busulfan conditioning, should be considered.

The issue of on-target and off-target unintended genetic modification was investigated by the Applicant and discussed at an advisory committee meeting. It appears impracticable to draw any conclusion in pre-marketing studies. The Applicant plans to investigate this issue further through the 15-year LTFU study (Study 131) for patients who received exa-cel in their clinical trials and a 15-year registry-based prospective observational study for patients who will receive commercial exa-cel. Please refer to review memos by other relevant review disciplines for more information.

10.2 Conclusions and Recommendations

Exa-cel is effective for prevention of protocol-defined severe vaso-occlusive crises in patient with severe sickle cell diseases. The limited sample size and follow-up duration of the interim analysis data package in this BLA limit assessment of the durability and the

robustness of the treatment effect in the single-arm trial. We will be able to assess these aspects more fully when the final analysis data package becomes available, which will include at least 24 months of follow-up for all exa-cel treated subjects. I have recommended that the review committee send an information request to the Applicant, stressing the importance of timely reporting of the final study results once all treated subjects in Study 121 have been followed up for 24 months, to enable a fuller assessment of the treatment effect.