



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From:	Srinivas S. Ayyala, MD Medical Officer, Pharmacovigilance Branch 1 PB1, DPV, OBPV, CBER, FDA
To:	Anna Kwilas, PhD Chair of the Review Committee Office of Therapeutic Products
Through:	Adamma Mba-Jonas, MD, MPH Branch Chief, PB1 Meghna Alimchandani, MD Deputy Director DPV OBPV, CBER, FDA
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Vertex Pharmaceuticals
Product:	CASGEVY (Exagamglogene autotemcel-exa-cel)
Application Type / Number	BLA / STN 125785/0
Approved Indication	Treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso-occlusive crises.
Proposed Indication	Treatment of transfusion dependent β -thalassemia (TDT) in patients 12 years and older.
Submission Date:	March 31, 2023
Action Due Date:	March 29, 2024

1 OBJECTIVE

Vertex Pharmaceuticals submitted an original BLA 125785/0 seeking licensure for a novel gene therapy product, CASGEVY™ (Exagamglogene autotemcel, for the proposed treatment of transfusion dependent β -thalassemia (TDT). The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) as well as to identify potential safety concerns that may require additional safety-related studies, should the product be approved.

2 BACKGROUND PRODUCT INFORMATION

2.1 Background

β -thalassemia is an autosomal recessive monogenetic disease, affecting more than 288,000 people worldwide, with another 60,000 infants born annually with the disease. Of these patients, 60-80% of the patients have a more severe form of the disease known as transfusion-dependent β -thalassemia (TDT), which requires regular red-cell transfusions and iron chelation for proper treatment of disease manifestations. In the United States and the European Union, the prevalence of TDT is estimated to be 15,000, with approximately 1500 infants born each year with the disease.¹

β -Thalassemia is caused by mutations resulting in a single nucleotide substitution, small deletions or insertions within the β -globin gene or its immediate flanking sequence, or in rare cases, gross deletions. These mutations result in reduced production of β -globin chains and HbA, leading to the accumulation of excess, unstable α -globin tetramers in erythroid cells, generating cytotoxic reactive oxidant species and cellular precipitates that impair the maturation and viability of red-cell precursors, resulting in ineffective erythropoiesis and premature hemolysis of circulating red cells.² The degree of imbalance between α -globin and β -globin chains impacts the severity of anemia, need for transfusions and clinical morbidity. The chronic nature of TDT is punctuated by ineffective erythropoiesis and peripheral hemolysis, leading to a state of chronic anemia. This anemia can result in growth and developmental delays, typical anemia-related symptoms such as fatigue, leg ulcers and can promote organ failure in adolescents and young adults. Complications secondary to peripheral hemolysis in β -thalassemia can induce a hypercoagulable state, manifesting as venous and arterial thrombosis, pulmonary hypertension, cerebrovascular events, and silent infarcts that increase with age.²

Approved therapies for TDT include red blood cell transfusion (target HgB = 9-10.5 g/dL) which aims to reduce the complications associated with chronic anemia, but carries the risk of iron overload, which can lead to multiple co-morbidities including transfusion related iron toxicity and viral infections,³ requiring the use of iron chelators for symptomatic improvement. Luspatercept, a more recently approved agent for the treatment of adults with transfusion-dependent β -thalassemia, is a recombinant fusion protein comprising a modified extracellular domain of the human activin receptor type IIB fused to the F_c domain of human IgG1. Together, the domains bind to select transforming growth factor β superfamily ligands, block SMAD2/3 signaling, and enhance erythroid maturation, ultimately reducing transfusion burden while decreasing serum ferritin levels without producing any clinically meaningful changes in liver or myocardial iron concentrations.² Allogenic hematopoietic stem cell transplant (HCST) has produced disease-free survival rates exceeding 90% in children with transfusion dependent β -thalassemia with favorable risk profiles and matched sibling donors, but the

¹ Biffi A. Gene Therapy as a Curative Option for β -Thalassemia. *N Engl J Med*. 2018;378(16):1551-1552. doi:10.1056/NEJMe1802169

² Taher AT, Musallam KM, Cappellini MD. β -Thalassemias. *N Engl J Med*. 2021;384(8):727-743. doi:10.1056/NEJMr2021838

³ Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia. *N Engl J Med*. 2018;378(16):1479-1493. doi:10.1056/NEJMoa1705342

procedure can be complicated by donor availability and the risk of graft-versus-host disease.^{3 4} Additionally, on August 17, 2022 the FDA approved betibeglogene autotemcel (Zynteglo™), a lentiviral vector based autologous hematopoietic stem-cell based gene therapy indicated for the treatment of adult and pediatric patients with TDT. While this therapy successfully achieved transfusion independence in most patients during clinical trials, insertional oncogenesis remains a potential risk that requires close monitoring.^{5 6}

2.2 Product Description

Casgevy™ (exagamglogene autotemcel or exa-cel) consists of autologous CD34+ human hematopoietic stem and progenitor cells (hHSPCs) modified by CRISPR-Cas9-mediated gene editing of the erythroid lineage-specific enhancer region of the BCL11A gene. This gene editing changes the DNA sequence in the autologous CD34+ hHSPCs, increasing the expression of γ -globin upon erythroid differentiation, allowing more HbF in adult erythroid cells, potentially leading to transfusion independence and the elimination of associated clinical complications.⁷

The process for receiving exa-cel starts with conditioning with busulfan to deplete highly proliferating hematopoietic stem progenitor cells (HSPC) residing in the bone marrow, thus making space and favoring engraftment of the autologous hematopoietic stem cells. Of note, common adverse events associated with busulfan include infection, hepatic veno-occlusive liver disease, seizures and hematologic abnormalities (e.g., thrombocytopenia, myelosuppression).⁸

Peripheral blood CD34+ HSPCs are retrieved by apheresis and mobilized into the bloodstream with filgrastim (G-CSF) and plerixafor at clinical sites to create (b) (4). Cells are (b) (4) isolated and undergo electroporation ex-vivo with Cas9-SPY101 ribonucleoprotein complex (consisting of the gene editing materials Cas9 nuclease (Cas9) and SPY101 sgRNA (SPY101) to create the exa-cel product. If the minimum dose of exa-cel is not met after initial medicinal product manufacturing, the patient undergoes additional cycles of mobilization and apheresis to obtain more cells for additional product manufacture. Each mobilization and apheresis cycle must be separated by a minimum of fourteen days, due to adverse events for plerixafor including tumor cell mobilization, thrombocytopenia, and splenomegaly.⁹

2.3 Proposed Dosing Regimen

CASGEVY™ is available as a cell suspension for a one-time intravenous infusion. The product requires thawing before use and 3×10^6 CD34+ cells per kg of body weight is infused, which may be composed of multiple vials. A patient is treated with a single administration of the product after mobilization, apheresis and myeloablative conditioning. CASGEVY™ must be administered between 48 hours and 7 days after the last dose of the myeloablative conditioning agent.

⁴ Xu, Yiqi, et al. "Affect of Age on Survival and Complications after Hematopoietic Stem Cell Transplantation in Children with β -Thalassemia Major." *Blood* 134 (2019): 4591.

⁵ Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non- β^0/β^0 Genotype β -Thalassemia. *N Engl J Med*. 2022;386(5):415-427. doi:10.1056/NEJMoa2113206

⁶ USPI for Zynteglo. Last Revised 2022.

⁷ Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β -Thalassemia. *N Engl J Med*. 2021;384(3):252-260. doi:10.1056/NEJMoa2031054

⁸ USPI for Busulfan. Last revised 1999.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020954s014lbl.pdf

⁹ USPI for Plerixafor. Last Revised 2008.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022311s001lbl.pdf

2.4 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125785 is:
Exagamglogene autotemcel (exa-cel; also known as Casgevy™) is a CRISPR/Cas9-modified autologous CD34+ hematopoietic stem and progenitor cell (HSPC) cellular therapy developed as a one-time treatment leading to a functional cure for patients with transfusion dependent β -thalassemia (TDT) in patients 12 years and older.

OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed upon indication after FDA review.

3 MATERIALS REVIEWED

Table 1: Materials Reviewed

Document	Module STN
Responses to Epidemiology Information Requests # 1-4	Module 1.11.3 of 125785/0
Annotated Prescribing Information	Module 1.14 of 125785/0
Risk Management Plan (Non-REMS) SCD and TDT Version 1.0	Module 1.16.1 of 125785/0
Request for Rare Pediatric Disease Review Voucher	Module 1.3.6 of 125785/0
Waiver of Pediatric Studies	Module 1.9.1 of 125785/0
Summary of Clinical Safety	Module 2.7.4 of 125785/0
Synopses of Individual Studies	Module 2.7.6 of 125785/0
Tabular Listing of Clinical Studies	Module 5.2 of 125785/0
D120 Safety Update (TDT)	Module 5.3.5.3 of 125785/0
CTX001-111 & 131-111-14-1-Tables D120 Safety Update	Module 5.3.5.3 of 125785/0
CTX001-111 & 131-111-14-3-4-Tables and Figures D120 Safety Update	Module 5.3.5.3 of 125785/0
CTX001-111-14-1-Epi IR # 1	Module 5.3.5.3 of 125785/0
CTX001-111-2-Ad hoc Table 2 and Listing 2 - Epi IR # 1	Module 5.3.5.3 of 125785/0
CTX001-111-14-3-1-Tables-Epi IR # 1	Module 5.3.5.3 of 125785/0
CTX001-111-14-3-2-Tables-Epi IR # 1	Module 5.3.5.3 of 125785/0
CTX001-111-14-3-4-Tables & Figures-Epi IR # 1	Module 5.3.5.3 of 125785/0
CTX001-111-14-3-5-Tables-Epi IR # 1	Module 5.3.5.3 of 125785/0
CTX001-111-14-3-6-Tables-Epi IR # 1	Module 5.3.5.3 of 125785/0
PASS Protocol VX22-290-101 Version 1.0	Module 5.3.6-2 of 125785/0

4 PERTINENT REGULATORY HISTORY

Casgevy™ was granted Orphan Drug Designation for treatment of β -thalassemia on April 28, 2020, and Rare Pediatric Disease Designation for treatment of β -thalassemia on September 28, 2020. The United Kingdom (U.K.) Medicines and Healthcare products Regulatory Agency (MHRA) granted conditional marketing authorization for the treatment of sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT) on November 16, 2023. The United States Food and Drug Administration (FDA) granted approval of the product for the treatment of sickle cell disease (SCD) on December 8, 2023.

5 DESCRIPTION OF CASGEVY CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical Studies

The clinical program for exa-cel consisted of two studies: one initial study (Study CTX001-111) and one long-term follow-up study (Study VX18-CXT001-131). OBPV defers to OTP on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our focused review of the applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125785/0 be approved. Please refer to the package insert for the final clinical safety data.

Table 2: Clinical Studies

Study	Description	Subject Description
CTX001-111 (Ongoing)	Single-arm, open-label, multi-site, single-dose, Phase 1/2/3 study of subjects aged 12-35.	<ul style="list-style-type: none">• Documented homozygous β-thalassemia (β^0/β^0-like) or compound heterozygous β-thalassemia including β thalassemia/hemoglobin E (HbE) (non-β^0/β^0-like)• A history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions 2 years before signing the ICF or the last rescreening (if applicable).• 59 subjects started mobilization at least once• 3 patients discontinued the study and were never dosed with exa-cel and 2 patients were not yet dosed with exa-cel at the time of the 120-day safety update• 54 patients were infused with exa-cel at the time of the 120-day safety update
VX18-CTX001-131 (Ongoing)	Multi-site, open-label, rollover study following patients enrolled in CTX001-111 for up to 15 years after exa-cel infusion.	<ul style="list-style-type: none">• 23 subjects completed the 2-year follow-up by the time of the 120-day safety update and rolled over from Study 111 to Study 131.

***Reviewer Comment:** There are two additional studies (VX21-CTX001-141 and VX21-CTX001-161) which are Phase 3 studies worldwide to review the safety and efficacy of exa-cel in subjects with TDT ages 2-11 (inclusive) and ages 12-35 (inclusive) respectively. However, there were no subjects in those studies at the initial data lock point and therefore, no safety data was submitted.*

6.2 Demographics

The study population of Study 111 consisted of 59 subjects who started the mobilization procedure (Safety Analysis Set or SAS) and 54 subjects who received exa-cel (Full Analysis Set or FAS). Three subjects discontinued the study (1 subject withdrew consent for undisclosed reasons, 1 subject did

not want to undergo a second apheresis procedure and 1 subject discontinued due to concerns with continued study participation) and were never dosed with exa-cel. Two additional patients were not yet dosed with exa-cel at the time of the 120-day safety update. The demographic characteristics of the Full Analysis Set is described below.

Table 3: Demographic Characteristics of Study 111 Subjects (From Table 14.1.3.1 in 120 Day Safety Data Update)

Category	FAS (N=54)
Gender (n, %)	
Male	29, 53.7%
Female	25, 46.3%
Age	
Median (years)	19.5
Mean (years)	21.3
Min, Max (years)	12, 35
Adolescent ≥ 12 and < 18 years (n, %)	19, 35.2 %
Adult ≥ 18 and ≤ 35 years (n, %)	35, 64.8 %
Race/Ethnicity (n, %)	
White	18, 33.3%
Black or African American	0
Asian	23, 42.6%
American Indian/Alaska Native	0
Native Hawaiian/Pacific Islander	0
Not Collected Local Regulations	8, 14.8%
Other	2, 3.7%
Multiracial	3, 5.6%

Reviewer comment: Subjects who received exa-cel were more likely to be adults of Asian or Caucasian descent, consistent with the global prevalence of beta thalassemia.

5.2 Summary of Treatment-Emergent Adverse Events (TEAEs)

All subjects in Study 111 experienced at least 1 TEAE. The TEAEs reported in >10% of subjects of either the SAS or FAS set are shown in Table A in the Appendix.

The most common (incidence>20%) TEAEs reported in the SAS set were nausea (n=26, 44.1%), headache (n=23, 39.0%), bone pain (n=20, 33.9%), vascular access site pain (n=17, 28.8%) and vomiting (n=12, 20.3%).

The most common (incidence>20%) TEAEs reported in the FAS set were febrile neutropenia (n=33, 61.1%), headache (n=30, 55.6%), stomatitis (n=28, 51.9%), thrombocytopenia (n=25, 46.3%), anaemia (n=24, 44.4%), nausea (n=23, 42.6%), mucosal inflammation (n=23, 42.6%), vomiting (n=22, 40.7%), platelet count decreased (n=21, 38.9%), hypokalemia (n=21, 38.9%), abdominal pain (n=20, 37.0%), epistaxis (n=20, 37.0%), arthralgia (n=19, 35.2%), constipation (n=18, 33.3%), neutrophil count decreased (n=16, 29.6%), diarrhoea (n=15, 27.8%), pyrexia (n=15, 27.8%), pruritus (n=15, 27.8%), decreased appetite (n=14, 25.9%), COVID-19 (n=14, 25.9%), petechiae (n=12, 22.2%), rash (n=12, 22.2%), alopecia (n=11, 20.4%) and pain in extremity (n=11, 20.4%).

There were no AEs leading to discontinuation or death.

Reviewer comment: The majority of the TEAEs reported in the SAS set prior to exa-cel infusion (such as nausea, headache, bone pain or vascular access site pain) are likely related to the known adverse events associated with the process of mobilization and apheresis, while the majority of the TEAEs reported in the FAS set after exa-cel infusion (such as febrile neutropenia, thrombocytopenia, anaemia, or mucosal inflammation) are likely related to the known adverse events associated with the busulfan conditioning regimen.

6.3 Serious Adverse Events (SAEs)

Table B in the Appendix reviews all the serious treatment-emergent adverse events (SAEs) that were reported in Study 111. The most common SAE reported in the SAS set was bacteraemia (n=2, 3.4%) while the most common SAE reported in the FAS set was veno-occlusive liver disease (n=5, 9.3%). There were no reported PTs that occurred in greater than 10% of the subjects. There were no deaths.

Reviewer Comment: The majority of the SAEs reported in the SAS set prior to exa-cel infusion (such as bacteraemia, bronchitis, viral gastroenteritis, nausea or vomiting) are likely related to the process of mobilization and apheresis, while the majority of the SAEs reported in the FAS set after exa-cel infusion (such as veno-occlusive liver disease, pneumonia, COVID-19, upper respiratory infection, hypoxia or thrombocytopenia) are likely related to the busulfan conditioning regimen.

6.4 Adverse Events of Special Interest

Platelet Engraftment Failure:

Platelet engraftment was defined as the first of three consecutive measurements on three separate days with platelets $\geq 20,000/\mu\text{L}$ without a platelet transfusion for seven consecutive days. For subjects discharged early, day seven after the last platelet transfusion was the day of platelet engraftment, as long as three subsequent and consecutive unsupported measurements on three different days were $\geq 20,000/\mu\text{L}$.

53 of 54 subjects who received exa-cel achieved platelet engraftment by the data cutoff, with a median time to engraftment of 44.0 days [range 20 – 200 days]. One subject who was pending platelet engraftment by the data cutoff date subsequently achieved platelet engraftment on study day 107.

Bleeding events were more common before platelet engraftment (n = 33, 61.1%) compared to after platelet engraftment (n = 11, 20.8%). Among the 26 subjects who achieved platelet engraftment by the median cutoff of 44.0 days, 18 subjects (69.2%) experienced an adverse bleeding event, with 6 of those subjects (23.1%) experiencing grade 3 bleeds and no bleeds classified as serious adverse events. Among the 18 subjects who achieved platelet engraftment after the median cutoff of 44.0 days, 18 subjects (66.7%) experienced an adverse bleeding events with 4 of those subjects (14.8%) experiencing grade 3 bleeds and 1 subject (3.7%) experiencing a CNS bleed (grade 4) that was classified as a serious adverse event.

Reviewer Comment: Median times to platelet engraftment were longer after exa-cel infusion as compared to allogeneic HSCT (approximately 30 days) but overall, there was no association between the incidence of bleeding events and time to platelet engraftment.

Neutrophil Engraftment Failure:

Neutrophil engraftment was defined as the first day of three consecutive measurements of absolute neutrophil count (ANC) $\geq 500/\mu\text{L}$ on three different days, achieved within 42 days post exa-cel infusion (Study Day 43), without use of unmodified CD34+ cells after reaching the nadir, defined as ANC $< 500/\mu\text{L}$.

53 of 54 subjects who received exa-cel achieved neutrophil engraftment by the data cutoff, with a median time to engraftment of 29.0 days [range: 12 – 56 days]. However, one subject did not achieve neutrophil engraftment until on Study Day 56, after the “failure” cutoff.

Among the 24 subjects who achieved neutrophil engraftment prior to Study Day 29, 18 subjects (75.0%) experienced an infection with 9 of those subjects (37.5%) experiencing infections classified as Grade 3 or higher and 7 subjects (29.2%) whose infections were classified as serious adverse events. Among the 30 subjects who achieved neutrophil engraftment after Study Day 29, 17 subjects (56.7%) experienced an infection with 6 of those subjects (20.0%) experiencing infections classified as Grade 3 or higher and 4 subjects (13.3%) whose infections were classified as serious adverse events.

Reviewer Comment: Median times to neutrophil engraftment were similar after exa-cel infusion as compared to allogeneic HSCT (approximately 30 days) and overall, there was no association between the incidence of infection and time to neutrophil engraftment.

Pregnancy:

Study 111 required that female subjects of childbearing potential were to use acceptable method(s) of contraception from consent through at least 6 months after exa-cel infusion based on busulfan product labeling. Male subjects were to use effective contraception from the start of mobilization through at least 6 months after exa-cel infusion. Both pregnant women and lactating female subjects were excluded from participation.

Reviewer Comment: No pregnancies of a female subject or a female partner of male subject were reported in Study 111.

6 SUMMARY OF PRIOR MARKET EXPERIENCE

This is a first-in-class product that has not yet been used outside of clinical trials in the US. As of January 15, 2024, there has been no global distribution of this product.

7 APPLICANT’S PHARMACOVIGILANCE PLAN

The sponsor submitted the original pharmacovigilance plan (PVP) for Exa-cel on March 31, 2023. Exa-cel was discussed during the Cellular, Tissue, and Gene Therapies Advisory Committee Meeting on October 31, 2023 in which the advisory committee provided input on testing strategies for the proposed post-market study, which was incorporated into additional recommendations for the PVP and Study Protocol VX22-290-101. The consolidated PVP for BLA 125785 and BLA 125787, CASGEVY US pharmacovigilance plan (PVP) for SCD and TDT Version 1.0, was received by the FDA on December 21, 2023 and is reviewed below.

The applicant’s proposed pharmacovigilance plan (PVP) is outlined in the table below.

Table 4: Pharmacovigilance Plan from Applicant Risk Management Plan

Type of Risk	Potential Safety Concern	Planned pharmacovigilance Activity
Identified	Delayed platelet engraftment	<ul style="list-style-type: none"> • Routine pharmacovigilance • Study VX22-290-101
Identified	Neutrophil engraftment failure	<ul style="list-style-type: none"> • Routine pharmacovigilance • Study VX22-290-101
Potential	Secondary malignancies due to off-target effects following genome editing	<ul style="list-style-type: none"> • Routine pharmacovigilance • Study VX22-290-101
Missing Information	Use in patients >35 years of age	<ul style="list-style-type: none"> • Study VX22-290-101
Missing Information	Use in patients < 12 years of age	<ul style="list-style-type: none"> • Study VX22-290-101
Missing Information	Long-term safety and efficacy	<ul style="list-style-type: none"> • Study VX22-290-101
Missing Information	Pregnancy (including partner pregnancy) and lactation	<ul style="list-style-type: none"> • Routine pharmacovigilance • Study VX22-290-101

Long term follow-up (LTFU) data from Study VX22-290-131 will also be important source of exa-cel safety data available in the post market period.

Routine Pharmacovigilance

Individual Case Safety Reports (ICSRs) from post marketing sources (spontaneous, solicited, literature, and regulatory authorities) will be collected, investigated, and submitted to the FDA as defined in 21 CFR 600.80. Submission of 15-day alert reports and periodic safety reports will proceed according to the reporting requirements delineated in 21 CFR 600.80(c). The applicant label provides instructions specific to the identified and potential risks, as well as missing information.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include specific adverse reaction follow-up questionnaires for delayed platelet engraftment, neutrophil engraftment failure, pregnancy and lactation and hematologic malignancies. These questionnaires will attempt to obtain more structured information on each topic in the post-approval setting.

In addition to follow-up questionnaires, all reports of pregnancy will be followed up at 6- and 12-months post birth for infant development details. Similarly, exposure during breast feeding will be reported and followed up if relevant findings are discovered. Any relevant findings will be discussed in aggregate reports.

Enhanced Pharmacovigilance

The sponsor describes processes for enhanced pharmacovigilance as below:

Expedited (15-day) reports will be submitted to the FDA for all adverse events of secondary malignancy with the exceptions of skin and cervical cancer. Additionally, periodic safety reports will include interval and cumulative safety assessments for all malignancies and events of off-target effects following genome editing from all available sources (e.g., post-market spontaneous and solicited reports, clinical studies), including a summary of any updates from Study 101.

Should a hematologic malignancy be reported, the following actions will be taken as part of a hematologic malignancy workup to evaluate any association with off-target genome editing:

- All relevant available information from the treating physician will be collected using a structured Hematologic Malignancy Information Collection Form. The diagnosis will be confirmed by expert review of the data and will be reported to the FDA as a secondary hematologic malignancy via expedited 15-day reporting.
- For each case of confirmed hematological malignancy, the sponsor will perform an investigation to evaluate if editing may have played a role. The investigation could include but is not limited to 1) evaluation of on-target editing in the malignant cells, 2) determination if off-target editing occurred, and 3) determination if pre-existing genomic drivers of hematologic malignancy were present in the patient sample. Stored sample from the patient may be tested for pre-existing genomic drivers of hematologic malignancies (e.g., via next-generation sequencing [NGS]).

The contribution of on- or off-target editing to the development of malignancy will be evaluated. Any on- or off-target edits that contributed to the hematologic malignancy will be reported to the Agency in an expedited manner.

Product Labeling

For delayed platelet engraftment, the Applicant's proposed United States Prescribing Information (USPI, Warnings and Precautions 5.2) and patient packet insert (PPI) includes:

- Recommendations for monitoring platelet counts and managing symptoms of bleeding.
- Patient advice on how to identify symptoms of low platelet counts and when to contact the doctor.

For neutrophil engraftment failure, the proposed United States Prescribing Information (USPI, Warnings and Precautions 5.1) and patient packet insert (PPI) includes:

- Recommendations for monitoring neutrophil counts and managing infections.
- Requirement for collection of backup CD34+ cells prior to myeloablative conditioning and infusion of exa-cel, so backup cells can be administered in the event of neutrophil engraftment failure.
- Patient advice on how to identify symptoms of low white blood cell counts and when to contact the doctor.
- Patient information on what to expect if engraftment fails.

For secondary malignancies due to off target effects following genome editing, the proposed United States Prescribing Information (USPI, Warnings and Precautions 5.1) includes:

- Warning that while not observed to date, the risk of unintended, off-target editing in CD34+ cells due to uncommon genetic variants cannot be ruled out and the clinical relevance of potential off-target editing remains unknown.

For pregnancy and lactation, the proposed USPI includes:

- Recommendations for contraception use, starting from mobilization through at least 6 months after administration of exa-cel.
- Confirmation of a negative pregnancy test prior to the start of each mobilization cycle and re-confirmation prior to myeloablative conditioning.
- Warning against administration of exa-cel during pregnancy due to risks associated with myeloablative conditioning.
- Warning that breastfeeding should be discontinued during conditioning due to potential risks associated with myeloablative conditioning.
- Advice to patients to discuss pregnancy and breast-feeding after exa-cel with the treating physician.

OBPV defers to OTP on final labeling decisions for the USPI.

Post Marketing Safety Study

FDA Guidance for Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020, available at <https://www.fda.gov/media/113768/download>) recommends 15-year long term follow up for gene editing products. In keeping with this Guidance, the sponsor proposed conducting a long-term registry study for patients receiving the product in the post-licensure setting (Study VX22-290-101) and continued LTFU of clinical trial participants who received the investigational product (Study VX22-290-131).

Table 5: Post-Marketing Study VX22-290-101

Study Name	Description
Long-term registry-based study of patients with transfusion dependent β - thalassemia (TDT) or sickle cell disease (SCD) treated with exagamglogene autotemcel (exa-cel) (VX22- 290-101).	A long-term, prospective observational cohort study designed to evaluate long- term outcomes of patients with TDT or SCD treated with exa-cel or allo-HSCT.

Patient Population

VX22-290-101 is an international post market observational cohort study following patients post-treatment. This study will include four cohorts:

- Patients who received exa-cel for treatment of β -thalassemia (β -thal Exa-cel Cohort)
- Patients who received exa-cel for treatment of SCD (SCD Exa-cel Cohort)
- Patients who received allogeneic HSCT for treatment of β -thalassemia (β -thal Allo-HSCT Comparator Cohort)
- Patients who received allogeneic HSCT for treatment of SCD (SCD Allo-HSCT Comparator Cohort)

Enrollment targets are 150 treated patients with TDT and 250 treated patients with SCD for a total of 400 exa-cel treated patients. The sponsor expects that the enrollment period for TDT patients will be between 3-5 years. It is anticipated that there will be an approximately equal number of allogeneic HSCT comparator patients enrolled. This study will have study sites in Germany, France, Italy, United Kingdom, and the United States.

Objectives

The objectives of the study are:

Primary

1. Evaluate long-term safety outcomes, including secondary malignancies and off-target effects of genome editing, in patients who received exa-cel for TDT or SCD.
2. Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT.

Secondary

1. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD.

2. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment TDT or SCD in comparison to patients receiving allo-HSCT.

Table 6: VX22-290-101 Milestones

Milestones	Planned Dates
Progress Reports	Q4 2025 - 2029
Interim Reports	Q4 2034/Q4 2039
Final Report	Q4 2044

Data Sources

Data will be collected from two existing international registries: the European Society for Blood and Marrow Transplantation (EBMT) Registry and the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. The Sponsor and registry operators jointly developed forms to specifically collect the study variables at time points 100 days, 6 months, 1 year, and annually thereafter. Site agreements will outline data collection responsibilities for the participating transplant centers.

Study Design

The safety variables that are collected in this observational registry are listed in Table 7:

Table 7: VX22-290-101: Safety Variables

Category	Variables
Primary Disease Diagnosis	<ul style="list-style-type: none"> • β-thalassemia diagnosis and genotype • SCD diagnosis and genotype
Exposure	<ul style="list-style-type: none"> • Transplant date (as Day 0) • Autologous HSCT with exa-cel infusion • Allogeneic HSCT infusion • Mobilization and conditioning regimen
Safety Outcomes	<ul style="list-style-type: none"> • Neutrophil recovery • Platelet recovery • New malignancy • New or worsening hematologic disorder • Mortality, cause
Effectiveness Outcomes	<ul style="list-style-type: none"> • Primary disease severity measures, including red blood cell transfusions and vaso-occlusive crisis episodes • Hemoglobin measures • Iron concentration measures • Disease-related end-organ damage / dysfunction • Iron overload management
Additional Key Variables	<ul style="list-style-type: none"> • Demographics • Health status • Transplant-related complications • Disease-related therapies • Additional laboratory measures • Pregnancy (with outcome)

Descriptive statistics will be presented for all study outcomes. Continuous variables will be summarized using the following descriptive summary statistics, where appropriate: the number of observations, mean, standard deviation, 95% CI, median, minimum value, maximum value, and 25th

and 75th percentile values. Categorical variables will be summarized using counts, percentages, and 95% CIs, as appropriate.

Long-term safety and effectiveness outcomes among exa-cel recipients will compare the post-transplant period to pre-transplant period, as well as comparisons between exa-cel recipients and their allo-HSCT comparator cohort.

Subgroup analyses will be performed by age group, genotype, and/or other patient characteristics, as appropriate. Ad-hoc statistical analyses may be performed, including modeling to adjust for differences in cohort characteristics and time to event analyses.

9. ANALYSIS OF APPLICANT'S PHARMACOVIGILANCE PLAN

9.1 Important Identified Risks

Delayed platelet engraftment:

Clinical trial data showed that time to engraftment did not have a clinically meaningful effect on the number of bleeding events experienced by the subjects. This identified risk is discussed in further detail under 5.2 of Warnings and Precautions of the product label, which recommends monitoring of platelet counts. Additionally, the product label will include a PPI with information on symptoms to watch for suggestive of low platelets and when to contact their providers. Risk of delayed platelet engraftment will be further characterized with assessments of platelet counts and recovery as part of Study VX22-290-101. The proposed pharmacovigilance plan for this risk is acceptable.

Neutrophil engraftment failure:

Although a single subject experienced neutrophil engraftment failure, clinical trial data showed that, overall, time to engraftment did not have a clinically meaningful effect on the number or type of infections experienced by the subjects. This identified risk is discussed in further detail under 5.1 of Warnings and Precautions of the product label, which recommends monitoring of absolute neutrophil counts (ANC). Additionally, the PPI will include information on symptoms to watch for and when to contact their providers. Neutrophil counts and recovery will also be assessed as part of Study VX22-290-101. The proposed pharmacovigilance plan for this risk is acceptable.

9.2 Important Potential Risks

Secondary malignancy and off-target effects following genome editing:

Though there are no cases of secondary malignancy in the clinical safety database to date; there remains a theoretical risk of secondary malignancies due to off-target genome editing effects. The OBPV and OTP review teams recommended a safety PMR studies to assess the serious risk of secondary malignancies and off-target effects following genome editing following treatment with exa-cel.

FDA guidance *Long Term Follow-Up After Administration of Human Gene Therapy Products* (January 2020) recommends that patients who receive genome editing products be followed for "up to fifteen years." Exa-cel, should it be approved, will be a first in class genome editing product.

The CBER Biologics Effectiveness and Safety (BEST) Program is not sufficient to assess the serious risk of secondary malignancy and off-target effects following genome editing in lieu of a post marketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). As per the 2019 draft guidance, Post marketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry, this determination "takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug)." Currently, the available data sources in the CBER BEST Program are not

sufficient to characterize the safety outcomes of secondary malignancy and other off-target effects following genome editing due to the need to collect tumor tissue for analysis and testing for off-target effects (including whole genome and/or exon sequencing). Additionally, the BEST Program does not include foreign data sources. Should there be future use of the product outside U.S., then the sponsor would likely need to access foreign data sources in addition to U.S. data sources, for assessment of such rare serious risks. A finding of insufficiency based on uncertainty at the time of approval is consistent with current guidance.

Sentinel insufficiency serves as a justification for requiring a safety-related post-marketing study under Section 901, Title IX of FDAAA. Therefore, if Exa-cel is approved, the Sponsor will be required to conduct two PMR safety studies under FDAAA Title IX to characterize the important potential risk of secondary malignancy and off-target effects following genome editing.

DPV/OBPV and OTP presented the need for two PMRs to the CBER Safety Working Group (SWG) on October 12, 2023:

- DPV recommended that the following LTFU study be conducted by the sponsor as a PMR: A post marketing, prospective, multi-center, observational study, to assess and characterize the risks of secondary malignancies and off-target effects following genome editing occurring after treatment with Exa-cel, and to assess the long-term safety of Exa-cel. The study will compare 250 sickle cell disease (SCD) patients and 150 transfusion dependent β -thalassemia patients (TDT) who received exa-cel to 250 SCD and 150 TDT patients who received allogeneic hematopoietic stem cell transplantation (HSCT). Each enrolled patient will be followed for 15 years after product administration and the study design will include monitoring at pre-specified intervals with adequate testing strategies as outlined in Study Protocol VX22-290-101).
- OTP recommended that the sponsor be required to conduct a bioinformatics study as a second PMR to further analyze off-target effects following genome editing. OBPV defers to the bioinformatics review memorandum and October 12, 2023 SWG meeting minutes for further details on the bioinformatics study.

The SWG concurred with the above recommendations for two post-marketing requirements (PMRs) to assess the serious risk of secondary malignancies and off-target effects following genome editing occurring after treatment with exa-cel. The sponsor notification that the post-marketing long-term follow-up observational study VX22-290-101 will be a PMR was issued on October 27, 2023. This notification required a post marketing, prospective, multi-center, observational cohort registry study, to assess and characterize the risks of secondary malignancies and off-target effects following genome editing occurring after treatment with exa-cel and to assess the long-term safety of exa-cel. The sponsor provided acknowledgment of the PMRs.

***Reviewer Comment:** While the PVP is acceptable, should the BLA be approved, the PMR protocol design and data analysis plan will be finalized with the sponsor post-licensure. OBPV plans to review the final study protocol upon submission and will continue to provide additional recommendations following the future submission of the full protocol for Study VX22-290-101.*

9.3 Missing Information

Use in patients >35 years of age:

In Study 111, exa-cel was not administered to patients over age 35. All subjects who received exa-cel during Study 111 will be monitored for up to 15 years in the long-term Study 131, which will allow collection of information after age 35 for some subjects. Additionally, Study VX22-290-101 will follow all registered patients for 15 years. The proposed pharmacovigilance plan for this missing information is therefore acceptable.

Use in patients <12 years of age:

In Study 111, exa-cel was not administered to patients under the age of 12. Since the current BLA indication does not include this population, no pharmacovigilance plan for this population was proposed. Should the sponsor wish to expand the product's indication to those under the age of 12, a revised pharmacovigilance plan must be submitted. Routine pharmacovigilance (assessment of any spontaneous reports of use in this population) is acceptable.

Pregnancy (including partner pregnancy) and lactation:

No pregnancies of a female subject or a female partner of a male subject nor any pregnancy-related adverse events were reported in Study 111. Providers will be instructed in the USPI to encourage the use of contraception and require a negative pregnancy test prior to administering exa-cel. The insufficient evidence related to pregnancy, lactation and reproductive potential will be discussed in the USPI under the "Use in Special Populations" sections of 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Males and Females of Reproductive Potential). All patients will have the opportunity to register for Study VX22-290-101 for long term monitoring, which may provide data on any subjects that do become pregnant or impregnate partners after receiving exa-cel. The proposed pharmacovigilance plan for this missing information is therefore acceptable.

10 DPV CONCLUSIONS

Given the use of novel gene-editing technology that has the potential to alter cellular DNA, DPV has determined that there are serious potential risks of secondary malignancy and off-target effects following genome editing associated with the use of this product. These potential risks warrant FDAAA Title IX post-marketing requirement (PMR) studies to characterize the safety of exa-cel more fully. The sponsor has proposed conducting a long-term follow up registry study for subjects treated with exa-cel (Study VX22-290-101) that will serve as one of the PMRs. This study will include the collection of tumor tissue for further analysis and genetic samples from patients which may include whole genome and exon sequencing; additional components of the study will be determined prior to finalization of the study protocol. A second PMR for a bioinformatics study is also planned and OBPV defers to OTP with respect to the bioinformatics study.

The review team determined that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary for this product. The risks of treatment with exa-cel will be mitigated through risk communication and risk minimization measures as recommended in the USPI as well as enhanced pharmacovigilance, should malignancies and off-target effects be detected following genome editing.

11 DPV RECOMMENDATIONS

Should this product be approved for TDT indication, OBPV/DPV recommends the following for the post-marketing safety monitoring of exa-cel (Casgevy):

- Routine pharmacovigilance activities proposed by the Applicant in the CASGEVY U.S. Pharmacovigilance Plan for SCD and TDT Version 1.0, with adverse event reporting as required under 21 CFR 600.80.
- Enhanced pharmacovigilance for secondary malignancy and off-target effects following genome editing: For 3 years following licensure, the Applicant will submit expedited (15-day) reports for all adverse events of secondary malignancy and off-target effects following genome editing, regardless of label status or seriousness. All relevant available information from the treating physician will be collected using a structured Hematologic Malignancy Information Collection Form. The diagnosis will be confirmed by expert review of the data and will be reported to the FDA as a secondary hematologic malignancy and hematologic workup of the malignancy will ensue to determine causative relationship with the product.

- In periodic safety reports, Applicant will include a safety assessment (based on interval and cumulative post-marketing safety data) for the risk of all secondary malignancies, and specifically for hematologic malignancies, and events of off-target effects following genome editing. This assessment will include a summary of any available interim reports for Study VX22-290-101.
- Safety-related post-marketing requirement (PMR) studies under 505 (o) of the FDCA: The review team and SWG have concurred with two FDAAA Title IX PMR studies to assess the unexpected serious risks of secondary malignancy and off-target effects following genome editing:
 - A post-marketing, prospective, multi-center, observational cohort registry study, to assess and characterize the risks of secondary malignancies and off-target effects following genome editing occurring after treatment with Exa-cel, and to assess the long-term safety of exa-cel in 150 TDT patients. Each enrolled patient will be followed for 15 years after product administration. The study design will include monitoring (at pre-specified intervals) with adequate testing strategies (Study Protocol VX22-290-101). DPV will review the final study protocol for VX22-290-101 when available. Please see the approval letter for the study milestone dates.
 - A bioinformatics study. OBPV defers to OTP for review of this study.

In addition to the above PMRs, the sponsor will also conduct additional follow-up of clinical trial participants under long term follow up Study VX22-290-131; OBPV defers to OTP on review of this study.

The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) at this time.

Please see the final version of the package insert submitted by the sponsor for the final agreed-upon content and language.

APPENDIX

Table A: Adverse Events Occurring in ≥ 10% of Subjects in Study 111 & Study 131 by SOC, PT Before and After Exa-cel Infusion (From Table 14.3.1.2.1 in 120 Day Safety Update)

System Organ Class (PT)	SAS (n=59) n (%)	FAS (n=54) n (%)	Cumulative (n=59) n (%)
Subjects with any AEs	56 (94.9%)	54 (100.0%)	58 (98.3%)
Blood & Lymphatic System Disorders	15 (25.4%)	49 (90.7%)	49 (83.1%)
Febrile Neutropenia	0	33 (61.1%)	33 (55.9%)
Thrombocytopenia	1 (1.7%)	25 (46.3%)	25 (42.4%)
Anaemia	10 (16.9%)	24 (44.4%)	27 (45.8%)
Neutropenia	0	9 (16.7%)	9 (15.3%)
Splenomegaly	1 (1.7%)	5 (9.3%)	6 (10.2%)
Gastrointestinal Disorders	36 (61.0%)	48 (88.9%)	51 (86.4%)
Stomatitis	2 (3.4%)	28 (51.9%)	28 (47.5%)
Nausea	26 (44.1%)	23 (42.6%)	35 (59.3%)
Vomiting	12 (20.3%)	22 (40.7%)	24 (40.7%)
Abdominal Pain	10 (16.9%)	20 (37.0%)	23 (39.0%)
Constipation	11 (18.6%)	18 (33.3%)	27 (45.8%)
Diarrhoea	6 (10.2%)	15 (27.8%)	19 (32.2%)
Abdominal Pain Upper	2 (3.4%)	8 (14.8%)	9 (15.3%)
Gastritis	0	6 (11.1%)	6 (10.2%)
Gingival Bleeding	0	6 (11.1%)	6 (10.2%)
Dyspepsia	2 (3.4%)	5 (9.3%)	6 (10.2%)
Toothache	2 (3.4%)	5 (9.3%)	7 (11.9%)
General Disorders and Administration Site Conditions	25 (42.4%)	44 (81.5%)	50 (84.7%)
Mucosal Inflammation	4 (6.8%)	23 (42.6%)	25 (42.4%)
Pyrexia	5 (8.5%)	15 (27.8%)	15 (25.4%)
Fatigue	7 (11.9%)	8 (14.8%)	14 (23.7%)
Asthenia	1 (1.7%)	7 (13.0%)	7 (11.9%)
Pain	5 (8.5%)	6 (11.1%)	10 (16.9%)
Oedema Peripheral	1 (1.7%)	5 (9.3%)	6 (10.2%)
Skin and Subcutaneous Tissue Disorders	9 (15.3%)	40 (74.1%)	42 (71.2%)
Pruritus	4 (6.8%)	15 (27.8%)	17 (28.8%)
Petechiae	0	12 (22.2%)	12 (20.3%)
Rash	1 (1.7%)	12 (22.2%)	12 (20.3%)
Alopecia	0	11 (20.4%)	11 (18.6%)
Rash Maculo-Papular	0	7 (13.0%)	7 (11.9%)
Skin Hyperpigmentation	0	6 (11.1%)	6 (10.2%)
Respiratory, Thoracic and Mediastinal Disorders	7 (11.9%)	39 (72.2%)	39 (66.1%)
Epistaxis	1 (1.7%)	20 (37.0%)	20 (33.9%)

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Cough	2 (3.4%)	10 (18.5%)	10 (16.9%)
Oropharyngeal Pain	2 (3.4%)	8 (14.8%)	10 (16.9%)
Hypoxia	1 (1.7%)	5 (9.3%)	6 (10.2%)
Infections and Infestations	15 (25.4%)	35 (64.8%)	41 (69.5%)
COVID-19	4 (6.8%)	14 (25.9%)	18 (30.5%)
Investigations	18 (30.5%)	35 (64.8%)	38 (64.4%)
Platelet Count Decreased	2 (3.4%)	21 (38.9%)	22 (37.3%)
Neutrophil Count Decreased	0	16 (29.6%)	16 (27.1%)
White Blood Cell Count Decreased	0	8 (14.8%)	8 (13.6%)
Alanine Aminotransferase Increased	5 (8.5%)	7 (13.0%)	9 (15.3%)
Aspartate Aminotransferase Increased	5 (8.5%)	7 (13.0%)	8 (13.6%)
International Normalised Ratio Increased	1 (1.7%)	7 (13.0%)	7 (11.9%)
Blood Alkaline Phosphatase Increased	4 (6.8%)	6 (11.1%)	9 (15.3%)
Blood Bilirubin Increased	3 (5.1%)	6 (11.1%)	8 (13.6%)
Gamma-glutamyltransferase Increased	2 (3.4%)	5 (9.3%)	6 (10.2%)
Nervous System Disorders	31 (52.5%)	35 (64.8%)	46 (78.0%)
Headache	23 (39.0%)	30 (55.6%)	40 (67.8%)
Dizziness	8 (13.6%)	8 (14.8%)	13 (22.0%)
Paresthesia	5 (8.5%)	2 (3.7%)	7 (11.9%)
Musculoskeletal and Connective Tissue Disorders	33 (55.9%)	33 (61.1%)	44 (74.6%)
Arthralgia	5 (8.5%)	19 (35.2%)	20 (33.9%)
Pain in Extremity	7 (11.9%)	11 (20.4%)	16 (27.1%)
Back Pain	11 (18.6%)	10 (18.5%)	18 (30.5%)
Bone Pain	20 (33.9%)	8 (14.8%)	25 (42.4%)
Neck Pain	8 (13.6%)	5 (9.3%)	11 (18.6%)
Muscle Spasms	3 (5.1%)	4 (7.4%)	7 (11.9%)
Metabolism and Nutritional Disorders	21 (35.6%)	32 (59.3%)	35 (59.3%)
Hypokalemia	11 (18.6%)	21 (38.9%)	24 (40.7%)
Decreased Appetite	0	14 (25.9%)	14 (23.7%)
Hypomagnesemia	7 (11.9%)	9 (16.7%)	14 (23.7%)
Hypophosphatemia	4 (6.8%)	9 (16.7%)	11 (18.6%)
Hypocalcemia	10 (16.9%)	7 (13.0%)	13 (22.0%)
Hyponatremia	4 (6.8%)	7 (13.0%)	9 (15.3%)
Fluid Retention	3 (5.1%)	4 (7.4%)	7 (11.9%)
Hyperglycemia	4 (6.8%)	3 (5.6%)	6 (10.2%)
Injury, Poisoning and Procedural Complications	27 (45.8%)	28 (51.9%)	37 (62.7%)
Procedural Pain	10 (16.9%)	8 (14.8%)	13 (22.0%)
Vascular Access Site Pain	17 (28.8%)	3 (5.6%)	19 (32.2%)
Psychiatric Disorders	8 (13.6%)	17 (31.5%)	22 (37.3%)
Insomnia	0	9 (16.7%)	9 (15.3%)
Anxiety	2 (3.4%)	5 (9.3%)	7 (11.9%)

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Eye Disorders	0	16 (29.6%)	16 (27.1%)
Vision Blurred	0	8 (14.8%)	8 (13.6%)
Renal and Urinary Disorders	5 (8.5%)	16 (29.6%)	19 (32.2%)
Haematuria	1 (1.7%)	7 (13.0%)	8 (13.6%)
Vascular Disorders	3 (5.1%)	16 (29.6%)	18 (30.5%)
Hypertension	0	6 (11.1%)	6 (10.2%)
Hypotension	3 (5.1%)	4 (7.4%)	6 (10.2%)
Cardiac Disorders	5 (8.5%)	14 (25.9%)	16 (27.1%)
Tachycardia	1 (1.7%)	8 (14.8%)	8 (13.6%)
Hepatobiliary Disorders	4 (6.8%)	14 (25.9%)	16 (27.1%)
Veno-occlusive Liver Disease	0	7 (13.0%)	7 (11.9%)
Hepatomegaly	1 (1.7%)	5 (9.3%)	6 (10.2%)
Reproductive System and Breast Disorders	2 (3.4%)	14 (25.9%)	16 (27.1%)
Ear and Labyrinth Disorders	0	6 (11.1%)	6 (10.2%)
Immune System Disorders	4 (6.8%)	6 (11.1%)	10 (16.9%)
Drug Hypersensitivity	4 (6.8%)	3 (5.6%)	7 (11.9%)

Table B: Serious Adverse Events of Subjects in Study 111 & Study 131 by SOC, PT Before and After Exa-cel Infusion (From Table 14.3.2.11 in 120 Day Safety Update)

System Organ Class (PT)	SAS (n=59) n (%)	FAS (n=54) n (%)	Cumulative (n=59) n (%)
Subjects with any SAEs	9 (15.3%)	19 (35.2%)	26 (44.1%)
Infections and Infestations	4 (6.8%)	11 (20.4%)	15 (25.4%)
Pneumonia	0	3 (5.6%)	3 (5.1%)
COVID-19	0	2 (3.7%)	2 (3.4%)
Upper Respiratory Tract Infection	0	2 (3.7%)	2 (3.4%)
Appendicitis	0	1 (1.9%)	1 (1.7%)
COVID-19 Pneumonia	0	1 (1.9%)	1 (1.7%)
Cholecystitis Infective	0	1 (1.9%)	1 (1.7%)
CMV Infection Reactivation	0	1 (1.9%)	1 (1.7%)
Gastroenteritis	0	1 (1.9%)	1 (1.7%)
Infection	0	1 (1.9%)	1 (1.7%)
Influenza	0	1 (1.9%)	1 (1.7%)
Klebsiella sepsis	0	1 (1.9%)	1 (1.7%)

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Lymphadenitis bacterial	0	1 (1.9%)	1 (1.7%)
Respiratory tract infection viral	0	1 (1.9%)	1 (1.7%)
Bacteraemia	2 (3.4%)	0	2 (3.4%)
Bronchitis	1 (1.7%)	0	1 (1.7%)
Gastroenteritis viral	1 (1.7%)	0	1 (1.7%)
Hepatobiliary disorders	1 (1.7%)	5 (9.3%)	6 (10.2%)
Veno-occlusive liver disease	0	5 (9.3%)	5 (8.5%)
Biliary colic	0	1 (1.9%)	1 (1.7%)
Hepatic siderosis	1 (1.7%)	0	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.7%)	5 (9.3%)	6 (10.2%)
Hypoxia	0	2 (3.7%)	2 (3.4%)
Acute respiratory distress syndrome	0	1 (1.9%)	1 (1.7%)
Acute respiratory failure	0	1 (1.9%)	1 (1.7%)
Idiopathic pneumonia syndrome	0	1 (1.9%)	1 (1.7%)
Respiratory distress	0	1 (1.9%)	1 (1.7%)
Paranasal cyst	1 (1.7%)	0	1 (1.7%)
Blood and lymphatic system disorders	0	3 (5.6%)	3 (5.1%)
Thrombocytopenia	0	2 (3.7%)	2 (3.4%)
Febrile neutropenia	0	1 (1.9%)	1 (1.7%)
Gastrointestinal disorders	1 (1.7%)	3 (5.6%)	4 (6.8%)
Anal fissure	0	1 (1.9%)	1 (1.7%)
Colitis	0	1 (1.9%)	1 (1.7%)
Constipation	0	1 (1.9%)	1 (1.7%)
Nausea	1 (1.7%)	1 (1.9%)	2 (3.4%)
Vomiting	1 (1.7%)	1 (1.9%)	2 (3.4%)
Abdominal pain lower	1 (1.7%)	0	1 (1.7%)
Nervous system disorders	0	3 (5.6%)	3 (5.1%)
Brain oedema	0	1 (1.9%)	1 (1.7%)
Cerebellar haemorrhage	0	1 (1.9%)	1 (1.7%)
Headache	0	1 (1.9%)	1 (1.7%)
Hydrocephalus	0	1 (1.9%)	1 (1.7%)
Loss of consciousness	0	1 (1.9%)	1 (1.7%)
Seizure	0	1 (1.9%)	1 (1.7%)
Subarachnoid haemorrhage	0	1 (1.9%)	1 (1.7%)
Injury, poisoning and procedural complications	0	2 (3.7%)	2 (3.4%)
Delayed engraftment	0	1 (1.9%)	1 (1.7%)
Vaccination complication	0	1 (1.9%)	1 (1.7%)

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Cardiac Disorders	0	1 (1.9%)	1 (1.7%)
Tachycardia	0	1 (1.9%)	1 (1.7%)
General disorders and administration site conditions	0	1 (1.9%)	1 (1.7%)
Pyrexia	0	1 (1.9%)	1 (1.7%)
Immune system disorders	1 (1.7%)	1 (1.9%)	2 (3.4%)
Haemophagocytic lymphohistiocytosis	0	1 (1.9%)	1 (1.7%)
Drug hypersensitivity	1 (1.7%)	0	1 (1.7%)
Vascular Disorders	0	1 (1.9%)	1 (1.7%)
Raynaud's phenomenon	0	1 (1.9%)	1 (1.7%)
Investigations	1 (1.7%)	0	1 (1.7%)
Alanine aminotransferase increased	1 (1.7%)	0	1 (1.7%)
Aspartate aminotransferase increased	1 (1.7%)	0	1 (1.7%)
Blood bilirubin increased	1 (1.7%)	0	1 (1.7%)
Metabolism and nutrition disorders	1 (1.7%)	0	1 (1.7%)
Dehydration	1 (1.7%)	0	1 (1.7%)
Hypokalemia	1 (1.7%)	0	1 (1.7%)
Hyponatremia	1 (1.7%)	0	1 (1.7%)
Renal and urinary disorders	2 (3.4%)	0	2 (3.4%)
Acute kidney injury	1 (1.7%)	0	1 (1.7%)
Nephrolithiasis	1 (1.7%)	0	1 (1.7%)
Reproductive system and breast disorders	2 (3.4%)	0	2 (3.4%)
Dysmenorrhoea	1 (1.7%)	0	1 (1.7%)
Ovarian cyst torsion	1 (1.7%)	0	1 (1.7%)

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