

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

PHARMACOVIGILANCE PLAN REVIEW FOR ORIGINAL BLA

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Subject: Review of Pharmacovigilance Plan

Applicant: Vertex Pharmaceuticals

Product: CASGEVY (exagamglogene autotemcel - exa-cel)

Application Number: BLA/ STN 125787/0

Proposed Indication: CASGEVY is a CRISPR/CAS9 modified autologous CD34+ hematopoietic stem and progenitor cell cellular therapy indicated for the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises.

Submission Date: November 22, 2022

Action Due Date: December 8, 2023

1 Objective

The sponsor, Vertex Pharmaceuticals, submitted an original BLA 125787/0 seeking licensure for a novel gene therapy product, Casgevy (exagamglogene autotemcel/exa-cel), for the proposed treatment of sickle-cell disease. This review assesses the adequacy of the pharmacovigilance plan proposed by the sponsor for postmarketing safety monitoring, and to identify potential safety concerns that may require additional postmarketing safety surveillance, studies, or other pharmacovigilance activities, should this product be approved.

2 Product Information

2.1 Background

Sickle cell disease (SCD) is an autosomal recessive monogenetic disease, affecting millions worldwide and over 100,000 people in the United States.¹ Patients have homozygous mutations in which a valine replaces a glutamic acid at position 6 in the β -globin protein which leads to polymerization of deoxygenated hemoglobin and red blood cell (RBC) sickling. The chronic nature of SCD is punctuated by recurrent vaso-occlusive crises (VOCs) with numerous complications that include acute pain, chronic hemolysis, anemia, acute chest syndrome, stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, limited growth, increased susceptibility to infections, fatigue, and progressive cognitive decline.² Approved therapies include hydroxyurea, which will reduce complications and number of VOCs by increasing production of fetal hemoglobin (HbF), but carries the risks of myelosuppression, malignancies, and teratogenesis.³ Allogeneic hematopoietic stem cell transplant (allo-HSCT) is the only known cure for SCD, but it can be difficult to find a matched donor, and the procedure runs the risk for graft-versus-host disease (GvHD).⁴

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, which allows more HbF in adult erythroid cells. As with hydroxyurea, the increase in HbF ameliorates the clinical complications of SCD.

The process for receiving Casgevy begins with conditioning with busulfan to deplete highly proliferating hematopoietic stem progenitor cells (HSPC) residing in the bone marrow (BM), thus making space and favoring engraftment of donor (in this case autologous) hematopoietic stem cells HSCs.⁵ Of note, common adverse events associated with busulfan include infections, hematologic abnormalities such as thrombocytopenia, myelosuppression and pulmonary dysfunction including bronchopulmonary dysplasia.

Peripheral blood CD34+ HSPCs are then mobilized into the bloodstream using Plerixafor and retrieved from patients with apheresis at clinical sites to create leukopaks. Cells are washed and 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 Casgevy product.

If the minimum dose of Casgevy 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 14 days, because the mobilization agents like Plerixafor increase the likelihood of vaso-occlusive crisis.⁶ Other known AEs for Plerixafor include tumor cell mobilization, thrombocytopenia, and splenomegaly.⁷ In addition, as a safety precaution to avoid crises, all subjects had RBC exchange or simple transfusions for a minimum of 8 weeks before starting mobilization. The transfusions are continued until busulfan conditioning, with the goal to maintain HbS level of <30% of total Hb while keeping total Hb concentration ≤ 11 g/dL. Subjects also receive an RBC exchange or simple transfusion within 3 days before the start of each mobilization/ apheresis cycle.

2.3 Proposed dosing regimen(s) and formulation(s)

Casgevy's proposed indication is for the treatment of sickle cell disease in patients 12 years and older with recurrent vaso occlusive crises. The minimum recommended dose of Casgevy is 3×10^6 CD34+ cells/kg. Casgevy is provided as a single dose for infusion containing a suspension of CD34+ cells in one or more vials.

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

3 Pertinent Regulatory History

Casgevy has not been marketed elsewhere in the world. Vertex Pharmaceuticals submitted the BLA application on November 3, 2022 and it received Orphan drug designation, which exempted them from PREA requirements, on May 11, 2020.

4 Materials Reviewed

Materials reviewed in support of this assessment are summarized in the table below.

Table 2: Materials Reviewed

Document	Module STN	Date Received
Nonclinical Overview	125787/0/0	Nov 3, 2022
Introduction	145787/0/2	Feb 24, 2023
Clinical Overview	125787/0/8	Apr 3, 2023
Pharmacovigilance Plan for Casgevy, Version 1.0	125787/0/8	Apr 3, 2023
Annotated Draft Labeling Text	125787/0/8	Apr 3, 2023
Summary of Clinical Safety	125787/0/8	Apr 3, 2023

Document	Module STN	Date Received
Interim Clinical Study Report	125787/0/8	Apr 3, 2023
Pharmacovigilance Plan for Casgevy, Version 1.0	125787/0/8	Apr 3, 2023
90-day safety update	125787/0/33	Jul 8, 2023
Clinical Overview Safety and Efficacy Update	125787/0/33	Jul 8, 2023
Table 14.3.1.1.1 Overview of Adverse Events Before and After CTX001 Infusion and Overall Safety Analysis Set	125787/0/33	Jul 8, 2023
Table 14.3.1.1.2 Overview of Adverse Events for Additional Study Intervals Safety Analysis Set	125787/0/33	Jul 8, 2023
Table 14.3.1.1.3 Overview of Adverse Events by Post-CTX001 Infusion Onset Time Intervals Safety Analysis Set	125787/0/33	Jul 8, 2023
Response to Information Request regarding vaso-occlusive crises that occurred prior to exa-cel infusion but after mobilization	125787/0/36	Jul 24, 2023
Response to Information Request for multiple revisions to PVP including adding delayed platelet engraftment failure as an identified risk and increasing sample size	125787/0/46	Aug 18, 2023
Pharmacovigilance Plan for Casgevy, Version 1.1	125787/0/46	Aug 18, 2023
Response to Information Request acknowledging PMR notification	125787/0/52	Nov 2, 2023
Response to Information Request for enhanced pharmacovigilance, updates to objectives, and testing strategies	125787/0/81	Nov 15, 2023
Pharmacovigilance Plan for Casgevy, Version 1.2	125787/0/81	Nov 15, 2023

5 Clinical Safety Database

The clinical program for Casgevy consisted of 2 studies: one initial study (Study CTX001-121) 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 125787/0 be approved. Please refer to the package insert for the final clinical safety data.

The table below describes these safety studies and their populations.

Table 3: Clinical program (Source: Interim Clinical Study Report)

Study	Description	Subjects Description
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CTX001-121 (ongoing)	Single-arm, open-label, multi-site, single-dose, Phase 1/2 study	<ul style="list-style-type: none"> Eligible subjects had documented βS/βS genotype who have severe SCD, are eligible for stem cell transplant, and do not require regular RBC transfusions. They were aged 12 to 35 years (inclusive) 63 subjects were enrolled at the time of the interim analysis 58 subjects started the mobilization procedure at least once 44 subjects were infused with exa-cel. As of DLP, 30 patients completed at least 18 months of follow up.
VX18-CXT001-131 (ongoing)	Multi-site, open-label, rollover study following patients enrolled in CTX001-121 for up to 15 years after exa-cel infusion	<ul style="list-style-type: none"> 8 subjects have rolled over from Study 121 to Study 131

Reviewer Comment: There is one additional study (VX21-CTX001-151) which is a Phase 3 study in the US and Italy to review the safety and efficacy of Casgevy in subjects ages 2-11 (inclusive) with severe SCD. However, there are no subjects in that study as of the data lock point, so no safety data was submitted.

5.1 Demographics:

The study population of Study 121 consisted of 58 subjects who began the mobilization procedure (referred to as the Safety Analysis Set, SAS) and 44 subjects who received Casgevy (referred to as the Full Analysis Set, FAS). Their demographic characteristics are described in the table below.

Table 4: Demographic characteristics of Study 121 subjects (Source: Table 14.1.3.1: Subject Demographics)

Category	SAS (n=58)	FAS (n=44)
Gender (n, %)		
Male	34, 58.6%	24, 54.5%
Female	24, 41.4%	20, 45.5%
Age		
Median (years)	22.0	20.0
Mean (years)	21.0	21.2
Min, Max (years)	12, 35	12, 34
Adolescent ≥ 12 and < 18 years (n, %)	13, 22.4%	12, 27.3%
Adult ≥ 18 and ≤ 35 years (n, %)	45, 77.6%	32, 72.7%
Race/Ethnicity (n, %)		
Asian	0, 0.0%	0, 0.0%

Black	50, 86.2%	38, 86.4%
Hispanic	2, 3.4%	2, 4.5%
White	4, 6.9%	3, 6.8%
Multiracial	0, 0.0%	0, 0.0%
Other	4, 6.9%	3, 6.8%

Reviewer comment:

Subjects who received Casgevy were more likely to be males, adults, and of the Black race. This is consistent with the increased known prevalence of sickle cell among Black Americans compared to other races.⁸ There are no reported differences in prevalence by sex,⁹ and the Sponsor did not comment why more males received Exacel than females. However, sex is unlikely to be a significant confounder for the adverse events reported.

5.2 Summary of All Treatment-Emergent Adverse Events (TEAEs)

All subjects in Study 121 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 Appendix A.

The 58 subjects in the SAS set had a median number of 2 mobilizations (range 1-6, average 2.45). The most common TEAEs reported in the SAS set were: nausea (n=44, 75.9%); vascular access site pain (n=28, 48.3%); sickle cell anaemia with crisis (n=25, 43.1%); vomiting (n=22, 37.9%); hypomagnesaemia, hypocalcaemia (n=20, 34.5% each); abdominal pain (n=19, 32.8%); constipation, headache (n=18, 31.0% each); paraesthesia (n=17, 29.3%); hypokalaemia, pruritus (n=14, 24.1% each); pain in extremity, procedural pain (n=13, 22.4% each); and pain (n=12, 20.7%).

The most common TEAEs reported in the FAS set were: nausea (n=31, 70.5%); stomatitis (n=28, 63.6%); vomiting (n=25, 56.8%); febrile neutropenia (n=24, 54.5%); abdominal pain, pruritis, headache (n=22, 50.0% each); platelet count decreased, decreased appetite (n=21, 47.7% each); constipation, pain in extremity (n=20, 45.5% each), arthralgia (n=19, 43.3%); pyrexia (n=18, 40.9%); diarrhoea, neutrophil count decreased (n=17, 38.6% each); fatigue, mucosal inflammation, anaemia, skin hyperpigmentation (n=16, 36.4% each); hypokalaemia, back pain (n=15, 34.1% each); neutropenia (n=13, 29.5%); thrombocytopenia, oedema peripheral (n=12, 27.3% each); abdominal pain upper, gastritis, pain, alanine aminotransferase increased, COVID-19 (n=11, 25.0% each); aspartate aminotransferase increased, skin exfoliation, neck pain, dizziness (n=10, 22.7% each); drug withdrawal syndrome, non-cardiac pain, CD4 lymphocytes decreased, hypomagnesaemia, oral candidiasis, procedural pain, epistaxis, oropharyngeal pain, anxiety, and tachycardia (n=9, 20.5% each).

The only AEs leading to discontinuation were related to the one death case discussed below.

Reviewer comment:

Many TEAEs prior to Casgevy infusion were related known adverse events associated with the process of mobilization and apheresis. These AE's include vascular access complications like pain, infections, and thromboses. The reviewer-assessed related TEAEs after Casgevy infusion were due to conditioning with Busulfan, and include infections, pain, and hematologic abnormalities such as thrombocytopenia and subsequent bleeds. No TEAEs were related to the Casgevy product itself.

5.3 Deaths

There was 1 death in Study 121. The subject presented with rhinorrhea and cough 70 days after receiving Casgevy. She was found to have grade 2 COVID-19, confirmed by a positive antigen test, and a chest X-ray showed bilateral pneumonia with patchy infiltrates and perihilar opacities. Though the COVID-19 infection was considered resolved in 20 days, the subject was hospitalized again 20 days later for pneumonia with hypoxia. At this point, the subject's chest CT scan showed multilobar ground glass infiltrates in an organizing pneumonia pattern and an echo showed moderate tricuspid regurgitation and mild pulmonary hypertension. However, COVID-19 PCR, blood culture, respiratory viral panel, autoimmune panel, and vasculitis markers were all negative.

The subject had a protracted course in the ICU including ECMO support, tension pneumothorax, shock liver, GI bleed with melena, AKI, limb ischemia, decubitus ulcer, volvulus and peritonitis, and septic shock. A transbronchial biopsy suggested lung injury related to busulfan and possibly COVID-19.

There were no deaths reported in Study 131.

Reviewer Comment:

The only death reported was after Casgevy infusion. As the patient first started having symptoms 70 days after infusion, it is unlikely that they were still immunocompromised from conditioning. However, there was evidence of lung injury from Busulfan that likely contributed to the patient's respiratory failure. COVID-19 was a confounding factor.

5.4 Other Serious Adverse Events (SAEs)

Table B in Appendix B reviews all the serious treatment-emergent adverse events (SAEs) that were reported in Studies 121 and 131. The most commonly reported SAEs (>10%), occurring prior to Casgevy infusion in the 58 subjects, were sickle cell anaemia with crisis (n=23, 39.7%) and acute chest syndrome (n=6, 10.3%). There were no reported PTs after Casgevy infusion that occurred in greater than 10% of subjects.

Reviewer Comment:

Many SAEs prior to Casgevy infusion, like pain, infection, and vaso-occlusive crises, were likely related to the process of mobilization and apheresis. Other reviewer-assessed related SAEs were likely related to conditioning with Busulfan, and include infections, pain, and hematologic abnormalities such as thrombocytopenia.

5.5 Adverse Events of Special Interest

Vaso-occlusive crises (VOCs)

10 subjects were identified who experienced serious VOCs within two weeks of initiating mobilization and apheresis.

The Sponsor was asked by FDA to conduct analyses to evaluate the frequency of VOCs and any association with the process of receiving Casgevy. Specifically, there were 18 VOCs in 12 subjects (20.7%) in the period prior to the start of plexifor mobilization compared to 23 VOCs in 14 subjects (24.1%) in the period after plexifor mobilization. The Sponsor felt this numerical difference was small and not clinically meaningful. Additionally, the Sponsor evaluated the occurrence of VOCs during the entire mobilization and apheresis period compared to the baseline period prior to enrollment. The baseline period of 2 years was divided into 6-month intervals to account for the variability of VOCs over time. Of the 58 subjects in the safety analysis set, only 2 had a higher annualized VOC rate during the entire mobilization and apheresis period compared to their 4 baseline rates (Subject (b) (6) 36.74 vs. 14; Subject (b) (6) 10.82 vs. 4). The Sponsor felt this represented “normal variability with respect to frequency of VOCs over time.”

Platelet engraftment failure

Day 7 after a subject's most recent platelet transfusion was designated as the day of platelet engraftment, as long as 3 subsequent and consecutive unsupported measurements on 3 different days were $\geq 50,000/\mu\text{L}$. All 44 subjects who received Casgevy achieved platelet engraftment by the data cutoff, with a median time to engraftment of 35.0 (range 23-126 days).

As expected, bleeding events were more common before platelet engraftment (n=15, 35.7%) compared to after platelet engraftment (n=6, 15.0%). Among 23 subjects who achieved platelet engraftment by the median cutoff of 35.0 days, 7 (35.0%) experienced non-serious bleeding events including one severe (grade 3 or higher) case of epistaxis and blood loss anemia; no serious bleeding AEs occurred. Among the 20 subjects who achieved platelet engraftment after the median cutoff of 35.0 days, 9 (45.0%) experienced bleeding events, include 2 AEs of Grade 3 severity – 1 subject experienced epistaxis on days 21 and 28 and 1 subject had the serious events of melena, gastric hemorrhage, and small intestinal hemorrhage. The latter subject was on ECMO at the time and their fatal case is discussed in detail in the death section.

Neutrophil engraftment failure

Neutrophil engraftment was defined as, “the first day of 3 consecutive measurements of absolute neutrophil count (ANC) $\geq 500/\mu\text{L}$ on 3 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 $< 500/\mu\text{L}$.” All subjects who received Casgevy (n=44, 100.0%) achieved neutrophil engraftment, with a median time to engraftment of 27.0 days (range 15-40 days).

Among the 21 subjects who achieved neutrophil engraftment prior to Study Day 27, 13 subjects (29.5%) had infection AEs, of which 5 (11.4%) had severe AEs (Grade 3 or higher), and 5 (11.4%) had SAEs. The SAEs included 3 cases of pneumonia, and 1 case each of sepsis (cause not identified), COVID-19, urinary tract infection, decubitus ulcer, and influenza like illness. Among the 19 subjects who achieved neutrophil engraftment on or after Study Day 27, 14 subjects (31.8%) had infection AEs, 5 (11.4%) of which had severe AEs, and 4 (9.1%) had SAEs. These SAEs were sepsis (in the setting of cholelithiasis), viral infection, diarrhea, dacrocystitis, and norovirus-related gastroenteritis.

Pregnancy

Study 121 required subjects to use two methods of birth control. Female subjects of childbearing potential had to agree to use these methods of contraception to avoid pregnancy from consent through at least 6 months after CTX001 infusion. Non-sterile male subjects of reproductive capacity who were or could become sexually active with female partners of childbearing potential had to agree to use these methods of contraception to avoid fathering a child from start of mobilization through at least 6 months after CTX001 infusion.

Both female subjects who became pregnant and male subjects' female partners who became pregnant during the study would be reported to the medical monitor and Vertex Global Patient Safety. They were followed through to outcome, and the infant was to be followed for 1 year after the birth, provided informed consent was obtained. Any AEs or SAEs occurring during pregnancy were reported and all reports of congenital abnormalities/birth defects or spontaneous miscarriages were considered SAEs. Elective abortions without complications were not considered AEs.

During the submitted clinical trial period, one subject became pregnant (Subject (b) (6) (b) (6) and two subjects impregnated their partners (subjects (b) (6) and (b) (6) (b) (6)). Their pregnancy courses are described below:

- Subject (b) (6) She became aware of her pregnancy within 3 months of her fourth mobilization/apheresis procedure. She elected to undergo a medical termination of pregnancy, which had no complications. A transvaginal ultrasound revealed no sonographic evidence or retained products of pregnancy and eventually her HCG result became negative.
- Subject (b) (6): At the time of the initial report, the subject's partner was thought to be 10 weeks pregnant. However, they did not consent to having their pregnancy followed.
- Subject (b) (6) The estimated date of conception in the partner occurred after the subject had undergone mobilization/apheresis once but before conditioning. The subject's partner had no reported maternal risk factors and an unremarkable pregnancy and delivery. She gave birth to a male weighing 3090 grams and 20 inches height. Birth outcome was reported as normal. At 6 months, infant's status was normal.

Reviewer Comment:

The analyses provided by the Sponsor show no clear change in the VOC rate compared to baseline. DPV agrees that the difference in VOC rate seen is likely not clinically meaningful.

Though platelet engraftment was achieved by all subjects, the median was significantly longer than what would be expected for allo-HSCT (typically closer to 30 days), whereas the median time to neutrophil engraftment occurred closer to the 30-day timeframe. However, the data for both neutrophil and platelet engraftment demonstrated no clinically meaningful differences related to time to engraftment.

Clinical trial data was provided for two pregnancy cases, one in a pregnant patient who underwent a termination with no complications and another whose partner had an unremarkable pregnancy, delivery, and birth outcome. More safety information is needed to assess the safety of Casgevy in pregnancy and lactation periods. This is especially important as the indication includes patients of childbearing age (12-35, inclusive).

6 Summary of Prior Marketed Experience

Not applicable. The product has not been previously approved or used outside of the clinical trials. This is a first in-class product.

7 Applicant's Pharmacovigilance Plan

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

Table 5: 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
Potential	Neutrophil engraftment failure	<ul style="list-style-type: none"> • Routine pharmacovigilance • Study VX22-290-101
Potential	Secondary malignancy	<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	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

Of note, long term follow up (LTFU) data from Study VX22-290-131 (LTFU for clinical trial participants who received the investigational product) will also be an important source of Casgevy safety data available in the postmarket period.

Routine Pharmacovigilance

Individual Case Safety Reports (ICSRs) from postmarketing 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 neutrophil engraftment failure and pregnancy and lactation. These questionnaires will obtain 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 will be required to conduct enhanced pharmacovigilance for all adverse events of secondary malignancy and off-target effects following genome editing as described above.

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 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 Casgevy 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.

Postmarketing 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 6: Postmarketing Study VX22-290-101

Study Name	Description
Long-term registry-based study of patients with β -thalassemia 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 SCD or β -thalassemia treated with Exa-cel or allo-HSCT

Patient Population

VX22-290-101 is an international postmarket 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 50 treated patients with β -thalassemia and 250 treated patients with SCD for a total of 300 exa-cel treated patients. The sponsor expects that the enrollment period for SCD patients will be up to approximately 3 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 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.

Secondary

1. Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of β -thalassemia or SCD
2. Evaluate long-term safety and effectiveness outcomes in patients who received exa-cel for treatment of β -thalassemia or SCD in comparison to patients receiving allo-HSCT

Table 7: VX22-290-101 Milestones

Milestone	Planned Dates
Final protocol submission	March 31, 2024
Study Completion Date	December 31, 2042
Final Report	December 31, 2043

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 8:

Table 8: 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

	<ul style="list-style-type: none"> • 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 Casgevy recipients will compare the post-transplant period to pre-transplant period, as well as comparisons between Casgevy 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.

Reviewer comment:

Subject enrollment goals and enrollment period for TDT patients in Study VX22-290-101 will be determined during the review cycle for (b) (4)

The statistical analysis plan and final protocol for Study VX22-290-101 are yet to be submitted. As subjects will need to voluntarily enroll in this registry, this study will not include information for subjects who do not volunteer to enroll, possibly introducing selection bias. Loss to follow-up will also result in missing information; the sponsor asserts that analyses will be performed to discern any systematic differences between patients who discontinued and patients who continued. The sponsor plans to adjust for potential differences in baseline characteristics of the Casgevy cohort and the allo-HSCT cohort in the study analyses.

More detailed analysis of the protocol will be performed when as subsequent versions are submitted.

8 Analysis of Applicant's Pharmacovigilance Plan

8.1 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.

8.2 Important Potential Risks

Neutrophil engraftment failure:

Clinical trial data showed that time to engraftment did not have a clinically meaningful effect on the number or type of infections experienced by the subjects. Though this potential risk did not occur during clinical trials, the product label recommends monitoring for absolute neutrophil count under 5.1 of Warnings and Precautions. 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.

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.” Casgevy, 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 postmarketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA). As per the 2019 draft guidance, *Postmarketing 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).” At this time, 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 Casgevy 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 postmarketing, 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 who received exa-cel to 250 patients who received allogeneic hematopoietic stem cell transplantation (HSCT), and 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).
- 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 PMRs to assess the serious risk of secondary malignancies and off-target effects following genome editing occurring after treatment with Exa-cel, and the Sponsor notification for the PMR for the LTFU observational study (Protocol VX22-290-101) was issued on October 27, 2023. that the post-marketing study will be a PMR. This notification required a postmarketing, 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 Casgevy and to assess the long-term safety of Casgevy (see DPV recommendations below). Notification of postmarketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) was issued on October 27, 2023 and the sponsor provided acknowledgment of the PMRs on November 2, 2023 (response received under STN 125787/0/76).

BLA 125787/0 was discussed during the Cellular, Tissue, and Gene Therapies Advisory Committee October 31, 2023 Meeting.¹⁰ The advisory committee provided input on testing strategies for the postmarket study, which were incorporated into additional recommendations for the PVP and the long-term follow-up safety study PMR (Study Protocol VX22-290-101) in an information request dated November 09, 2023. This requested the following:

- 1) Enhanced pharmacovigilance:
 - a) The sponsor 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.
 - b) In periodic safety reports:
 - i) Include a safety assessment (based on interval and cumulative postmarketing safety data) for the risk of all secondary malignancies, and specifically for hematologic malignancies, and events of off-target effects following genome editing. Sponsor assessments should specify the data sources for reports of secondary malignancy or events of off-target effects following genome editing (i.e., clinical trial data, or data from postmarketing safety study, or data from postmarketing spontaneous reports).
 - ii) Include a summary of any available interim reports for Study VX22-290-101.
- 2) Updates to the PVP:
 - a) Include “secondary malignancies and off-target effects following genome editing” as an important potential risk; with routine and enhanced pharmacovigilance, and evaluation as a safety concern in sponsor LTFU studies VX18-CTX001-131 and VX22-290-101. This is in accordance with the FDA guidance on Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020), which recommends 15-year long-term follow up for gene editing products.
 - b) Include “use in patients <12 years of age” as missing information with routine pharmacovigilance
- 3) Updates to study protocol VX22-290-101
 - a) Reflect the change in milestones based on the request for an increased sample size of 250 SCD patients treated with exa-cel.
 - i) To reflect this increase in sample size, updates to the anticipated date for completion of your enrollment period.
 - ii) This revision should include changes to the expected dates for interim analysis (IA) reports (IA1 after enrollment completion, IA2 after 5 years of follow up after enrollment, and IA3 after 10 years of follow up). Please also plan to submit a summary of any available interim reports in your periodic safety reports as applicable (and provide acknowledgement for this request).
 - b) Indicate the minimum frequency with which data will be transferred from the registries (CIBMTR and EBMT) to Vertex.
 - c) Modification of the primary objective from “Evaluate long-term safety outcomes in patients who received exa-cel for treatment of β -thalassemia or SCD” to “Evaluate long-term safety outcomes, **including secondary malignancies and off-target effects of genome editing**, in patients who received exa-cel”
 - d) Monitoring (at pre-specified intervals) with adequate testing strategies:
 - i) i. Baseline:
 - (1) 1. Obtain complete blood count (CBC) with differential, pathologic review of peripheral blood smear, and bone marrow biopsy (core and aspirate) for comprehensive pathology review, to include: flow cytometry, conventional karyotyping, and NGS molecular panel - as appropriate for age and including coverage for gene mutations expected in myeloid and lymphoid malignancies.

- (2) 2. FISH should be performed if karyotyping or CBC is abnormal.
- ii) ii. Perform CBC at least every 4 months for the first two years, then annually or as clinically indicated.
- iii) iii. NGS and bone marrow biopsy and aspirate post exa-cel should be performed in subjects with abnormal blood counts

The Sponsor agreed to all of the requested changes, except request 3(d). OBPV is continuing to discuss adequate testing strategies with the Sponsor. Should the BLA be approved, the PMR protocol design and data analysis plan will be discussed with the Applicant post licensure. OBPV will review the final study protocol upon submission to ensure that the recommendations on study design were appropriately incorporated. We plan to communicate with the sponsor, that while we acknowledge their response to Epidemiology Information Request #4, dated November 9, 2023, FDA's agreement on their proposed testing strategies and data collection for the postmarketing requirement Study VX22-290-101 will be deferred until our review of the full protocol. FDA will provide additional recommendations following the future submission of the full protocol for Study VX22-290-101.

The sponsor response, including an updated PVP (version 1.2) was acceptable (IR response received under STN 125787/0/81).

8.3 Missing Information

Use in patients >35 years of age:

In the clinical trials, Casgevy was not administered to patients over age 35. All subjects who received Casgevy during Study 121 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, the registry Study VX22-290-101 will follow all registered patients for 15 years. The proposed pharmacovigilance plan for this missing information is acceptable.

Use in patients <12 years of age:

In the clinical trials, Casgevy was not administered to patients over under the age of 12. As the current BLA indication does not include this population, no pharmacovigilance plan 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. The proposed pharmacovigilance plan for this missing information is acceptable.

Long-term safety:

Subjects from Study 121 will continue to be monitored in Study 131 for long term follow up. Although follow-up data is limited at this time (the goal of the LTFU study is to include 15-year follow up), there has been no significant safety events associated with Exacel after its infusion seen within the initial two years. Furthermore, all patients will have the opportunity to register for Study VX22-290-101 for further safety monitoring as discussed above. The proposed pharmacovigilance plan for this missing information is acceptable.

Pregnancy (including partner pregnancy) and lactation:

Three pregnancies occurred during the clinical trial period. The outcome for one is missing and another elected for medical termination, so only one live birth was reported. No pregnancy-related adverse events were reported. Providers will be instructed in the USPI to encourage the use of contraception and require a negative pregnancy test prior to administering Casgevy. The insufficient evidence related to pregnancy, lactation, and reproductive potential will be discussed in the USPI under 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Males and Females of Reproductive Potential) with the Use in Special Populations section. All patients will have the opportunity to register for Study VX22-290-101 for long term monitoring which may provide for collection of data on any subjects that do become pregnant or impregnate partners after receipt of Casgevy. The proposed pharmacovigilance plan for this missing information is acceptable.

9 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 use of this product. These potential risks warrant FDAAA Title IX post-marketing requirement (PMR) studies to more fully characterize the safety of Casgevy. The sponsor has proposed to conduct a long-term follow up registry study for subjects treated with Casgevy (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; OBPV defers to OPT on 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 Casgevy 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 following genome editing be detected.

10 DPV RECOMMENDATIONS

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

- 1) Routine pharmacovigilance activities proposed by the applicant in the Pharmacovigilance Plan, with adverse event reporting as required under 21 CFR 600.80.
- 2) Enhanced pharmacovigilance for secondary malignancy and off-target effects following genome editing:

- The sponsor 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.
 - In periodic safety reports, include a safety assessment (based on interval and cumulative postmarketing safety data) for the risk of all secondary malignancies, and specifically for hematologic malignancies, and events of off-target effects following genome editing. Include a summary of any available interim reports for Study VX22-290-101.
- 3) Safety-related postmarketing 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 risk of secondary malignancy and off-target effects following genome editing:
- A postmarketing, 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 Casgevy and to assess the long-term safety of Casgevy. The study plans to compare 250 sickle cell disease (SCD) patients who received exa-cel to 250 patients who received allogeneic hematopoietic stem cell transplantation (HSCT), and 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 A

Table A: Adverse Events Occurring in $\geq 10\%$ of Subjects of Study 121 by SOC, PT Before and After Exacel Infusion (From Table 14.3.1.2.1 in 90 Day Safety Update)

System Organ Class Preferred Term	SAS (n=58) n (%)	FAS (n=44) n (%)	Cumulative (n=58) n (%)
Blood and lymphatic system disorders	27 (46.6)	43 (97.7)	49 (84.5)
Febrile neutropenia	0 (0)	24 (54.5)	24 (41.4)
Anemia	3 (5.2)	16 (36.4)	18 (31.0)
Neutropenia	0 (0)	13 (29.5)	13 (22.4)
Thrombocytopenia	2 (3.4)	12 (27.3)	13 (22.4)
Sickle cell anaemia with crisis	25 (43.1)	6 (13.6)	26 (44.8)
Lymphopenia	0 (0)	5 (11.4)	5 (8.6)
Gastrointestinal disorders	47 (81.0)	41 (93.2)	50 (86.2)
Nausea	44 (75.9)	31 (70.5)	47 (81.0)
Stomatitis	0 (0)	28 (63.6)	28 (48.0)
Vomiting	22 (37.9)	25 (56.8)	33 (56.9)
Abdominal pain	19 (32.8)	22 (50.0)	31 (53.4)
Constipation	18 (31.0)	20 (45.5)	29 (50.0)
Diarrhoea	7 (12.1)	17 (38.6)	22 (37.9)
Abdominal pain upper	2 (3.4)	11 (25.0)	13 (22.4)
Gastritis	1 (1.7)	11 (25.0)	12 (20.7)
Gastroesophageal reflux disease	0 (0)	8 (18.2)	8 (13.8)
Dyspepsia	4 (6.9)	5 (11.4)	8 (13.8)
Haematochezia	0 (0)	5 (11.4)	5 (8.6)
Paraesthesia oral	7 (12.1)	1 (2.3)	8 (13.8)
General disorders and administration site conditions	28 (48.3)	41 (93.2)	48 (82.8)
Pyrexia	7 (12.1)	18 (40.9)	23 (39.7)

Mucosal inflammation	7 (12.1)	16 (36.4)	19 (32.8)
Fatigue	0 (0)	16 (36.4)	16 (27.6)
Oedema peripheral	3 (5.2)	12 (27.3)	13 (22.4)
Pain	12 (20.7)	11 (25.0)	19 (32.8)
Drug withdrawal syndrome	0 (0)	9 (20.5)	9 (15.5)
Non-cardiac chest pain	5 (8.6)	9 (20.5)	10 (17.2)
Chest pain	2 (3.4)	6 (13.6)	7 (12.1)
Investigations	20 (34.5)	39 (88.6)	43 (74.1)
Platelet count decreased	4 (6.9)	21 (47.7)	21 (36.2)
Neutrophil count decreased	0 (0)	17 (38.6)	17 (29.3)
Alanine aminotransferase increased	4 (6.9)	11 (25.0)	13 (22.4)
Aspartate aminotransferase increased	4 (6.9)	10 (22.7)	12 (20.7)
CD4 lymphocytes decreased	0 (0)	9 (20.5)	9 (15.5)
International normalized ratio increased	0 (0)	8 (18.2)	8 (13.8)
Weight decreased	0 (0)	8 (18.2)	8 (13.8)
Blood alkaline phosphatase increased	1 (1.7)	6 (13.6)	7 (12.1)
White blood cell count decreased	0 (0)	6 (13.6)	6 (10.3)
Blood bilirubin increased	4 (6.9)	4 (9.1)	8 (13.8)
Metabolism and nutrition disorders	34 (58.6)	33 (75.0)	43 (74.1)
Decreased appetite	6 (10.3)	21 (47.7)	25 (43.1)
Hypokalaemia	14 (24.1)	15 (34.1)	21 (36.2)
Hypomagnesaemia	20 (34.5)	9 (20.5)	24 (41.4)
Hyperphosphataemia	2 (3.4)	6 (13.6)	8 (13.8)
Hypocalcaemia	20 (34.5)	1 (2.3)	21 (36.2)
Skin and subcutaneous tissue disorders	19 (32.8)	33 (75.0)	43 (74.1)
Pruritis	14 (24.1)	22 (50.0)	33 (56.9)
Skin hyperpigmentation	0 (0)	16 (36.4)	16 (27.6)

Skin exfoliation	0 (0)	10 (22.7)	10 (17.2)
Alopecia	0 (0)	7 (15.9)	7 (12.1)
Dry skin	1 (1.7)	6 (13.6)	7 (12.1)
Nervous system disorders	35 (60.3)	29 (65.9)	45 (77.6)
Headache	18 (31.0)	22 (50.0)	31 (53.4)
Dizziness	5 (8.6)	10 (22.7)	13 (22.4)
Paraesthesia	17 (29.3)	5 (11.4)	19 (32.8)
Infections and Infestations	21 (36.2)	29 (65.9)	40 (69.0)
COVID-19	6 (10.3)	11 (25.0)	16 (27.6)
Oral candidiasis	0 (0)	9 (20.5)	9 (15.5)
Pneumonia	1 (1.7)	7 (15.9)	7 (12.1)
Upper respiratory tract infection	1 (1.7)	5 (11.4)	6 (10.3)
Musculoskeletal and connective tissue disorders	29 (50.0)	29 (65.9)	36 (65.5)
Pain in extremity	13 (22.4)	20 (45.5)	26 (44.8)
Arthralgia	10 (17.2)	19 (43.2)	22 (37.9)
Back pain	15 (25.9)	15 (34.1)	22 (37.9)
Neck pain	5 (8.6)	10 (22.7)	10 (17.2)
Bone pain	5 (8.6)	6 (13.6)	11 (19.0)
Myalgia	2 (3.4)	4 (9.1)	6 (10.3)
Injury, poisoning, and procedural complications	37 (63.8)	24 (54.5)	42 (72.4)
Procedural pain	13 (22.4)	9 (20.5)	15 (25.9)
Transfusion reaction	3 (5.2)	3 (6.8)	6 (10.3)
Vascular access site pain	28 (48.3)	2 (4.5)	30 (51.7)
Respiratory, thoracic, and mediastinal disorders	19 (32.8)	24 (54.5)	35 (60.3)
Epistaxis	3 (5.2)	9 (20.5)	10 (17.2)
Oropharyngeal pain	3 (5.2)	9 (20.5)	12 (20.7)
Cough	6 (10.3)	7 (15.9)	12 (20.7)
Dyspnoea	2 (3.4)	4 (9.1)	6 (10.3)
Acute chest syndrome	7 (12.1)	0 (0)	7 (12.1)

Reproductive system and breast disorders	6 (10.30)	19 (43.2)	21 (36.2)
Vascular disorders	10 (17.2)	1 (38.6)	23 (39.7)
Hypertension	3 (5.2)	7 (15.9)	10 (17.2)
Hot flush	0 (0)	5 (11.4)	5 (8.6)
Hypotension	6 (10.3)	3 (6.8)	8 (13.8)
Psychiatric disorders	9 (15.5)	17 (38.6)	22 (37.9)
Anxiety	5 (8.6)	9 (20.5)	13 (22.4)
Insomnia	2 (3.4)	7 (15.9)	8 (13.6)
Depression	2 (3.4)	4 (9.1)	6 (10.3)
Eye disorders	3 (5.2)	17 (38.6)	18 (31.0)
Vision blurred	0 (0)	6 (13.6)	6 (10.3)
Renal and urinary disorders	2 (3.4)	12 (27.3)	13 (22.4)
Dysuria	0 (0)	7 (15.9)	7 (12.1)
Hepatobiliary disorders	6 (10.3)	12 (27.3)	16 (27.6)
Cholelithiasis	2 (3.4)	8 (18.2)	10 (17.2)
Cardiac disorders	4 (6.9)	10 (22.7)	12 (20.7)
Tachycardia	2 (3.4)	9 (20.5)	10 (17.2)
Ear and labyrinth disorders	1 (1.7)	7 (15.9)	8 (13.8)
Immune system disorders	4 (6.9)	3 (6.8)	6 (10.3)

* The study population of Study 121 consisted of 58 subjects who began the mobilization procedure (referred to as the Safety Analysis Set, SAS) and 44 subjects who received Casgevy (referred to as the Full Analysis Set, FAS).

Appendix B:

Table B: Treatment-Emergent Serious Adverse Events by SOC, PT Before and After Exacel Infusion (Source: Table 14.3.2.1.1 from Interim Clinical Study Report)

System Organ Class Preferred Term	SAS (n=58) n (%)	FAS (n=44) n (%)	Cumulative (n=58) n (%)
Infections and infestations	15 (25.9)	9 (20.5)	21 (36.2)
Pneumonia	1 (1.7)	4 (9.1)	5 (8.6)
Sepsis	1 (1.7)	2 (4.5)	3 (5.2)
COVID-19	1 (1.7)	1 (2.3)	2 (3.4)
Dacryocystitis	0 (0)	1 (2.3)	1 (1.7)
Septic shock	0 (0)	1 (2.3)	1 (1.7)
Urinary tract infection	0 (0)	1 (2.3)	1 (1.7)
Viral infection	0 (0)	1 (2.3)	1 (1.7)
Bacteraemia	2 (3.4)	1 (2.3)	2 (3.4)
Catheter site cellulitis	1 (1.7)	0 (0)	1 (1.7)
Device related infection	1 (1.7)	0 (0)	1 (1.7)
Influenza	2 (3.4)	0 (0)	2 (3.4)
Klebsiella sepsis	1 (1.7)	0 (0)	1 (1.7)
Periorbital cellulitis	1 (1.7)	0 (0)	1 (1.7)
Staphylococcal bacteraemia	2 (3.4)	0 (0)	2 (3.4)
Upper respiratory tract infection	1 (1.7)	0 (0)	1 (1.7)
Vascular device infection	3 (5.2)	0 (0)	3 (5.2)
Viral upper respiratory tract infection	1 (1.7)	0 (0)	1 (1.7)

Gastrointestinal disorders	5 (8.6)	6 (13.6)	9 (15.5)
Abdominal pain	4 (6.9)	3 (6.8)	5 (8.6)
Constipation	0 (0)	3 (6.8)	3 (5.2)
Abdominal pain upper	1 (1.7)	2 (4.5)	3 (5.2)
Diarrhoea	0 (0)	1 (2.3)	1 (1.7)
Nausea	1 (1.7)	0 (0)	1 (1.7)
General disorders and administration site conditions	7 (12.1)	5 (11.9)	11(19.0)
Pyrexia	2 (3.4)	3 (6.8)	5 (8.6)
Non-cardiac chest pain	0 (0)	2 (4.5)	2 (3.4)
Pain	1 (1.7)	2 (4.5)	3 (5.2)
Fatigue	1 (1.7)	1 (2.3)	2 (3.4)
Influenza like illness	0 (0)	1 (2.3)	1 (1.7)
Catheter site pain	1 (1.7)	0 (0)	1 (1.7)
Chest pain	1 (1.7)	0 (0)	1 (1.7)
Vascular device occlusion	2 (3.4)	0 (0)	2 (3.4)
Hepatobiliary disorders	3 (5.2)	5 (11.4)	8 (13.8)
Cholelithiasis	2 (3.4)	4 (9.1)	6 (10.3)
Cholecystitis	0 (0)	1 (2.3)	1 (1.7)
Bile duct stone	1 (1.7)	0 (0)	1 (1.7)
Respiratory, thoracic, and mediastinal disorders	9 (15.5)	4 (9.1)	13 (22.4)
Oropharyngeal pain	0 (0)	2 (4.5)	2 (3.4)

Dyspnoea	0 (0)	1 (2.3)	1 (1.7)
Epistaxis	0 (0)	1 (2.3)	1 (1.7)
Hypoxia	1 (1.7)	1 (2.3)	2 (3.4)
Respiratory failure	0 (0)	1 (2.3)	1 (1.7)
Acute chest syndrome	6 (10.3)	0 (0)	6 (10.3)
Pulmonary embolism	2 (3.4)	0 (0)	2 (3.4)
Blood and lymphatic system disorders	23 (39.7)	4 (9.1)	24 (41.4)
Sickle cell anaemia with crisis	23 (39.7)	3 (6.8)	24 (41.4)
Febrile neutropenia	0 (0)	1 (2.3)	1 (1.7)
Eye disorders	0 (0)	2 (4.5)	2 (3.4)
Periorbital oedema	0 (0)	1 (2.3)	1 (1.7)
Vision blurred	0 (0)	1 (2.3)	1 (1.7)
Cardiac disorders	0 (0)	1 (2.3)	1 (1.7)
Tachycardia	0 (0)	1 (2.3)	1 (1.7)
Investigations	0 (0)	1 (2.3)	1 (1.7)
Platelet count decreased	0 (0)	1 (2.3)	1 (1.7)
Injury, poisoning, and procedural complications	6 (10.3)	2 (4.5)	7 (12.1)
Gun shot wound	0 (0)	1 (2.3)	1 (1.7)
Procedural pain	0 (0)	1 (2.3)	1 (1.7)
Apheresis related complication	1 (1.7)	0 (0)	1 (1.7)
Intentional overdose	1 (1.7)	0 (0)	1 (1.7)

Transfusion reaction	1 (1.7)	0 (0)	1 (1.7)
Vascular access complication	1 (1.7)	0 (0)	1 (1.7)
Vascular access site discharge	1 (1.7)	0 (0)	1 (1.7)
Musculoskeletal and connective tissue disorders	7 (12.1)	1 (2.3)	8 (13.8)
Back pain	4 (6.9)	1 (2.3)	5 (8.6)
Arthralgia	1 (1.7)	0 (0)	1 (1.7)
Bone pain	2 (3.4)	0 (0)	2 (3.4)
Flank pain	1 (1.7)	0 (0)	1 (1.7)
Neck pain	1 (1.7)	0 (0)	1 (1.7)
Osteonecrosis	1 (1.7)	0 (0)	1 (1.7)
Pain in extremity	1 (1.7)	0 (0)	1 (1.7)
Nervous system disorders	5 (8.6)	1 (2.3)	6 (10.3)
Migraine	1 (1.7)	1 (2.3)	2 (3.4)
Dizziness	1 (1.7)	0 (0)	1 (1.7)
Haemorrhage intracranial	1 (1.7)	0 (0)	1 (1.7)
Headache	1 (1.7)	0 (0)	1 (1.7)
Metabolic encephalopathy	1 (1.7)	0 (0)	1 (1.7)
Psychiatric disorders	3 (5.2)	1 (2.3)	4 (6.9)
Anxiety	2 (3.4)	1 (2.3)	3 (5.2)
Depression	1 (1.7)	1 (2.3)	2 (3.4)
Drug dependence	1 (1.7)	1 (2.3)	2 (3.4)
Suicide attempt	1 (1.7)	0 (0)	1 (1.7)

Skin and subcutaneous tissue disorders	0 (0)	1 (2.3)	1 (1.7)
Decubitus ulcer	0 (0)	1 (2.3)	1 (1.7)
Vascular disorders	3 (5.2)	1 (2.3)	4 (6.9)
Deep vein thrombosis	1 (1.7)	1 (2.3)	2 (3.4)
Hypotension	1 (1.7)	0 (0)	1 (1.7)
Jugular vein thrombosis	1 (1.7)	0 (0)	1 (1.7)
Immune system disorders	1 (1.7)	0 (0)	1 (1.7)
Anaphylactic reaction	1 (1.7)	0 (0)	1 (1.7)
Neoplasm benign, malignant, and unspecified (including cysts and polyps)	1 (1.7)	0 (0)	1 (1.7)
Nasal neoplasm benign	1 (1.7)	0 (0)	1 (1.7)
Reproductive system and breast disorders	1 (1.7)	0 (0)	1 (1.7)
Priapism	1 (1.7)	0 (0)	1 (1.7)

* The study population of Study 121 consisted of 58 subjects who began the mobilization procedure (referred to as the Safety Analysis Set, SAS) and 44 subjects who received Casgevy (referred to as the Full Analysis Set, FAS).

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