Module 1.8.2

EU RISK MANAGEMENT PLAN

For Casgevy (exagamglogene autotemcel [exa-cel])

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(transfusion-dependent β-thalassemia and sickle cell disease)

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Not applicable		

QPPV Name: Jan Petracek, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ACS	acute chest syndrome
Allo	allogeneic
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Auto	autologous
AVN	avascular necrosis
BCL11A	B-Cell Lymphoma/Leukemia 11A
BMD	bone mineral density
cGy	centigray
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	cytomegalovirus
CRISPR-Cas9	clustered regularly interspaced short palindromic repeats-associated 9 nuclease
CSSCD	Cooperative Study of Sickle Cell Disease
Cy	cyclophosphamide
DLco	lung diffusing capacity for carbon monoxide
DMSO	dimethyl sulfoxide
EBMT	European Group for Blood and Marrow Transplantation
EMA	European Medicines Agency
exa-cel	exagamglogene autotemcel (Tradename Casgevy)
EU	European Union
GT	gene therapy
GVHD	graft-versus-host disease
Hb	Haemoglobin
HbA	adult haemoglobin
HbF	foetal haemoglobin
HbS	sickle haemoglobin
HbSC	βS/βC genotype
HCP	healthcare professional
hHSPCs	human haematopoietic stem and progenitor cells
HLA	human leukocyte antigen
HR	hazard ratio
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplant
HSPCs	haematopoietic stem and progenitor cells
IV	intravenous
LV	left ventricle
MA	marketing authorisation
MDS	myelodysplastic syndrome
N	number of subjects
NSG	NOD/SCID/IL2Rγnull
NR	not reported
PASS	post-authorisation safety study
PCR	polymerase chain reaction
PL	Package Leaflet
PSUR	periodic safety update report
PV	pharmacovigilance

Abbreviation	Definition
PY	person- or patient-years
PT-Cy	post-transplant cyclophosphamide
r-ATG	rabbit-anti-thymocyte globulin
RBC	red blood cells
RMP	Risk Management Plan
RNA	ribonucleic acid
SAE	serious adverse event
SCA	sickle cell anaemia
SCD	sickle cell disease
SD	standard deviation
sgRNA	single guide RNA
SmPC	Summary of Product Characteristics
SOB	specific obligation
SOC	system organ class
SPY101-RNP	gRNA Cas9 ribonucleoprotein
TBI	total body irradiation
TDT	transfusion-dependent β-thalassemia
TLI	total lymphoid irradiation
UK	United Kingdom
US	United States
USA	United States of America
USPI	United States Prescribing Information
VOC	vaso-occlusive crisis
VOD	veno-occlusive liver disease
WHO	World Health Organization

PART I Product Overview

Active substance(s)	exagamglogene autotemcel (exa-cel)
Pharmacotherapeutic group(s) (ATC Code)	B06AX05
Market Authorisation Applicant	Vertex Pharmaceuticals (Ireland) Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Casgevy
Market authorisation procedure	centralised
Brief description of the product	Casgevy is a genetically modified autologous $CD34^+$ cell enriched population that contains human haematopoietic stem and progenitor cells (HSPCs) edited ex vivo by CRISPR/Cas9 at the erythroid-specific enhancer region of the *BCL11A* gene. Cas9 is an enzyme that uses CRISPR single guide RNA (sgRNA) sequences to cleave a specific genomic locus that is complementary to the CRISPR sgRNA.
	The permanent, highly specific edit from Casgevy treatment results in the reduction of *BCL11A* gene transcription, which in turns leads to γ-globin expression and, upon erythroid differentiation, an increase in levels of foetal haemoglobin (HbF), thereby ameliorating effects of decreased or absent β-globin in transfusion-dependent β-thalassemia (TDT) and dysfunctional β-globin in sickle cell disease (SCD).
Hyperlink to the Product Information	(Proposed) Summary of Product Characteristics for Casgevy
Indication(s) in the EEA	**Current (if applicable)**: Not applicable
	Proposed: Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available. Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.
Dosage in the EEA	**Current (if applicable):** Not applicable
	Proposed (if applicable): Casgevy is a one-time, single-dose, intravenously administered cellular suspension of autologous product at a recommended minimum dose of 3×10^6 $CD34^+$ cells/kg.
Pharmaceutical form(s) and strengths	**Current (if applicable):** Not applicable
	Proposed: The medicinal product is packaged in one or more vials overall containing a dispersion of 4 to 13×10^6 cells/mL of viable $CD34^+$ cells enriched population suspended in a cryopreservative solution. Each vial contains 1.5 to 20 mL of Casgevy.
Is/will the product be subject to additional monitoring in the EU	Yes

PART II Safety Specification

SI Epidemiology of Indications and Target Populations

Casgevy (exagamglogene autotemcel [exa-cel]) therapy is administered as part of an autologous haematopoietic stem cell transplant (HSCT) procedure and indicated for the treatment of patients with transfusion dependent β-thalassemia (TDT) or sickle cell disease (SCD). This module discusses the:

- Disease epidemiology for TDT (Section SI.1),
- Disease epidemiology for SCD (Section SI.2), and
- Common risks and complications associated with myeloablative conditioning and the HSCT procedure (Section SI.3).

SI.1 Transfusion-dependent β-thalassemia

β-thalassemia is caused by genetic mutations that reduce or eliminate the expression of β-globin, which results in an α- to non-α-globin chain imbalance and decrease in adult haemoglobin (HbA) tetramers in red blood cells (RBCs). Unpaired α-globin chains precipitate, leading to destruction of erythroid precursors and ineffective erythropoiesis (i.e., destruction of RBC precursors in the bone marrow) and peripheral haemolysis.[1] TDT is the most severe form of β-thalassemia and is characterised by very severe anaemia requiring regular transfusions. Frequent transfusions can lead to iron overload with related complications that include diabetes and other endocrine diseases, cardiomyopathy, and liver fibrosis and cirrhosis, whereas insufficient transfusion therapy can be responsible for growth retardation, skeletal abnormalities, leg ulcers, and spleen and liver enlargement due to extra-medullary haematopoiesis.[2-8] Symptoms of TDT first become apparent as early as 6 months of age as foetal haemoglobin (HbF) decreases and can be fatal in early life if untreated.

Despite the severity of TDT, reliable disease frequency and epidemiology data are limited and vary by region. In the following sections, estimates from different data sources are shown, including sources that discuss all severities of β-thalassemia and not just TDT.

SI.1.1 Incidence

In 2008, WHO estimated about 25,511 patients with TDT are born globally each year (Table 1).[9]

Table 1 Estimated Annual Births for β-Thalassemia and TDT, by Region

	Estimated Annual Births[b]	
WHO Regions[a]	**β-Thalassemia**	**TDT**
Africa	1,386	1,278
American	341	255
Eastern Mediterranean	9,914	9,053
European	1,019	920
Southeast Asian	20,420	9,983
Western Pacific	7,538	4,022
Global	**40,618**	**25,511**

Source: Modell et al.[9]
TDT: transfusion-dependent β-thalassemia; WHO: World Health Organization
[a] Where data are available.
[b] All values are minimum estimates.

SI.1.2 Prevalence

The exact global prevalence of TDT is unknown. According to 2008 WHO estimates, there were 97,630 known patients with β-thalassemia globally, including all disease phenotypes and not limited to TDT.[9]

Table 2 presents the estimated prevalence of β-thalassemia globally and by country or region, with TDT estimates provided where available.

Table 2 Estimated Prevalence of β-Thalassemia, by Region

		Estimated Prevalence	
Region / Country	**Source[a]**	**β-thalassemia**	**TDT**
UK	National Haemoglobinopathy Registry, 2020[10]	1,484	1,045
Europe	Deep, 2020; Agouti, 2019[11]; Angastiniotis, 2021[12]; Conte, 2016[13]; Cancho, 2020[14]	9,200+	2,300+
US	Lal 2021[15]	2,600	NR
Middle East	Angastiniotis, 2021[16]; Alsaeed, 2018[17]; Kadhim, 2017[18]; Rajab, 2000[19]; Hossain, 2022[20]	82,000+	10,900+
Global	**WHO, 2008[9]**	**97,630**	**Not reported**

TDT: transfusion-dependent β-thalassemia; UK: United Kingdom; US: United States; WHO: World Health Organization

[a] Where data are available.

SI.1.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Risk factors for the disease

β-thalassemia is a genetic disease, therefore discussion of risk factors is not applicable.

Age at diagnosis

β-thalassemia is present at birth though clinical onset generally occurs between 6 and 24 months of age. In industrialised countries, infants affected by β-thalassemia are often diagnosed at birth through newborn screening programmes.[21]

Age distribution among prevalent patients

Data from the UK National Haemoglobinopathy Registry[22] suggests that individuals with thalassemia living in developed nations may live to age 70 years and older, though the median age is approximately 25 to 35 years.

Sex

β-thalassemia is passed on to offspring through autosomal recessive inheritance. The incidence of β-thalassemia is approximately equivalent between male and female sexes.

Race / ethnic origin

β-thalassemia is a disorder that is highly linked to ethnicity and is often associated with individuals originating from the Mediterranean, the Middle East, South Asia, and Southeast Asia.[21]

SI.1.4 Main Existing Treatment Options

The main existing treatment options for TDT are primarily directed at preventing complications of the disease and are not curative; these include chronic blood transfusions,

iron chelation, and other medications. These non-curative treatment options and associated risks are summarised in Table 3.

Table 3 Main Existing Non-Curative Options in TDT

Treatment Option	Risks
Blood Transfusions	
• Chronic lifelong blood transfusions deliver healthy RBCs to the circulatory system to correct anaemia and are the mainstay of therapy for patients with TDT.[23] Transfusions are often initiated before the age of 1 year and are typically administered every 3 to 4 weeks.	• Regular blood transfusions can cause excess iron to build up in the body resulting in damage to vital organs, especially the heart and the liver. Organ damage due to iron build up leads to additional complications such as abdominal pain, weakness, fatigue, and joint pain.[24-26] • Transfusion-related complications also include transfusion-transmitted infections.[27-29] • RBC alloimmunisation is a continuing, clinically significant risk among individuals receiving regular blood transfusions.[30]
Iron Chelation	
• Chelation therapy (e.g., deferoxamine, deferiprone, deferasirox) is essential to mitigate the toxicities of transfusion-related iron overload. • A study using US and UK patients from the Thalassemia Clinical Research Network found that over 95% of patients were on some type of chelation therapy.[31]	• Chelation agents are associated with various toxicities, including visual, gastrointestinal, and haematologic disorders.[23]
Reblozyl (luspatercept)[32]	
• Erythroid maturation agent for the treatment of anaemia in TDT patients	• Thromboembolic events were reported in 3.6% of luspatercept-treated patients in BELIEVE.

TDT: transfusion-dependent β-thalassemia; UK: United Kingdom; US: United States

Allogeneic HSCT is a potentially curative option for TDT; however, its availability is generally limited to patients who have a matched stem cell donor, which is only approximately 25% to 30% of patients eligible for HSCT. There were 281 transplants for thalassemias reported to the European Bone Marrow Transplant (EBMT) Patient Registry in 2020[33], whereas about 45 transplants for TDT were reported in the US.[34] In addition, the procedure is associated with significant risks (e.g., graft versus-host disease), as discussed fully in Section SI.3.

SI.1.5 Natural History of the Indicated Condition in the Untreated Population

Mortality

Without regular transfusions, TDT patient survival is poor, with approximately 85% dying by five years of age due to severe anaemia.[2]

Even with optimal care including access to regular transfusions and iron chelation therapy, the overall survival of a patient with TDT is significantly reduced compared to people without the disease, with only 65% surviving to age 50 years.[35]

The annual mortality rate in the TDT population was estimated to range from 2.9% in 2007 to 0.7% in 2011 in a study of 454 patients from Taiwan.[36] Similar findings were reported from the multi-national Thalassemia Longitudinal Cohort study of 327 TDT patients, with a mortality rate of 6.3 per 1000 person-years (PY; or 0.6% annually).

The causes of death in TDT are mainly related to iron overload, which has been implicated in over 90% of deaths. Cardiomyopathy secondary to iron deposition in the heart has been

reported as the main cause of death induced by transfusion-related iron overload in patients with TDT.[23, 31, 37-39] For instance, in a study from Greece[38], cardiac disease accounted for 71.3% of all deaths and in an Italian study;[37] 50.8% of deaths were due to heart failure and 6.6% due to arrhythmia.

Morbidity

β-thalassaemia is associated with numerous, progressive complications in nearly every organ system due to anaemia and iron overload. Chronic anaemia leads to reduced growth and development, and haemolysis leads to damage of the vasculature, thrombosis, and pulmonary hypertension.[40] Iron overload from transfusions leads to cardiomyopathy, liver fibrosis and cirrhosis, and endocrinopathies in adolescents and adults. These and other complications are discussed in more detail in Section SI.1.6.

SI.1.6 Important Complications and Comorbidities

Complications of β-thalassemia include those related to the disease itself as well as those associated with the available treatment options (e.g., transfusions, iron chelation).

SI.1.6.1 Hypersplenism

Patients with β-thalassemia are susceptible to hypersplenism due to increased red blood cell destruction. In the Thalassemia Clinical Research Network registry comprising patients from the USA and Canada, 55% of 342 patients with TDT underwent splenectomy at a median age of 9 years.[41]

SI.1.6.2 Pulmonary Hypertension

Pulmonary hypertension has been reported in 10% to 75% of patients with TDT; associated risk factors include severity of haemolysis, older age, splenectomy, prothrombotic state, and iron overload.[42]

SI.1.6.3 Cardiac Complications

Cardiac iron overload and heart disease (e.g., arrhythmia, heart failure) are prevalent in the TDT population.

The frequency of severe cardiac iron overload in patients with TDT was reported to range from 13% to 46%.[43]

The overall pooled prevalence of cardiac complications was 42% in a systematic review and meta-analyses of the literature evaluating TDT patients worldwide.[44]

SI.1.6.4 Liver Complications

Liver iron overload can cause hepatocyte damage, fibrosis, and eventually cirrhosis, particularly in the context of concurrent hepatitis C or hepatitis B virus infections.[25] The interacting effects of iron toxicity and viral infections increase the risk of hepatocellular carcinoma.

Liver diseases of varying severity were noted in 20% of TDT patients in Germany.[26]

Frequent transfusions put patients at risk of transfusion-transmitted infections, including viral hepatitis. Across studies in thalassemia patients, 0.3% to 6.5% of patients were reported to be hepatitis B surface antigen positive and 2.0% to 85.2% were positive for anti-hepatitis C antibodies.[27-29]

SI.1.6.5 Renal Complications

Tubular dysfunction with proteinuria and glomerular filtration rate abnormalities are not uncommon in patients with β-thalassemia.[45]

Abnormalities in the kidney could be caused by anaemia, iron-mediated toxicity, or chelation therapy.[45] Deferoxamine is associated with kidney injury only when administered intravenously at high doses, and orally administered deferasirox is associated with dose-dependent increases in serum creatinine and proteinuria.[46]

In a study of TDT or β-thalassemia intermedia patients who received regular transfusions, creatinine clearance was in the normal range for most regularly transfused subjects, but 8% had an abnormally low clearance. Significant proteinuria affects an estimated 20% to 33% of adult patients with TDT.[47]

SI.1.6.6 Endocrinopathies

Endocrinopathies (e.g., diabetes, hypothyroidism, hypogonadism) are common in regularly transfused patients with TDT.[36, 37, 41, 48]

At least 1 endocrine condition is expected to develop in children with TDT before they reach the age of 10 years and the majority of adults are expected to have at least 1 form of endocrine dysfunction, with hypogonadism being the most frequent.[26, 49]

For instance, in an Italian study of 165 adult patients with TDT, 73.3% had any form of endocrinopathy, 9.7% had diabetes, 39.4% had hypothyroidism, and 65.5% had hypogonadism at baseline.[49] Over the course of 5 years of follow-up, the prevalence of any endocrinopathy further increased by about 1.2%.

SI.1.6.7 Malignancy

As TDT patients are living longer lives dues to optimisation of transfusion programmes and implementation of iron chelation regimens, a new set of complications, such as cancers are being diagnosed as patients age.[50]

A large nationwide cohort study from Taiwan[51] (Table 4) showed that relative to the general population, patients with any form of thalassemia had a higher incidence of cancers, including more than 5 times higher risk of haematologic malignancy and almost 2 times higher risk of abdominal cancers. Furthermore, patients with the most severe form of disease, TDT, had more than 7 times higher risk of any cancers, and more than 9 times higher risk of haematological and abdominal cancers compared to thalassemia patients who did not receive transfusions. Although risk factors that promote cancer development among TDT patients have not been fully elucidated, iron overload and transfusion-related infections could be contributing factors.[50-52]

Table 4 Cancer Incidence in a Large Population of Thalassemia Patients, Taiwan

Cancer Type	Thalassemia Population (N=2,655)		TDT Sub-Population (N=130)	
	Incidence Rate per 1,000 PY	Adjusted HR (95% CI) vs. General Population	Incidence Rate per 1,000 PY	Adjusted HR (95% CI) vs. Thalassemia without Transfusion
Any	3.96	1.54 (1.15-2.07)	25.10	6.70 (3.29-13.6)
Haematologic	0.60	5.32 (2.18-13.0)	4.56	9.31 (1.46-59.3)
Abdominal	1.55	1.96 (1.22-3.15)	14.80	9.12 (3.09-27.0)

Table 4 Cancer Incidence in a Large Population of Thalassemia Patients, Taiwan

Source: Study using data from Taiwan Longitudinal Health Insurance Database[51]
CI: confidence interval; HR: hazard ratio; PY: person-years; TDT: transfusion-dependent β-thalassemia

SI.1.6.8 Bone Disease

Low bone mineral density, a precursor to osteopenia and osteoporosis, is a common complication of thalassemia. Together, osteopenia and osteoporosis affect 40% to 50% of patients with TDT.[53]

SI.2 Sickle Cell Disease

SCD is an inherited group of haematological disorders characterised by the production of sickle haemoglobin (HbS), a structural variant of normal HbA.[54]

The sickle β-globin mutation can be heterozygous (e.g., HbAS) or homozygous (HbSS). HbSS individuals experience a severe shortage of healthy RBCs leading to acute and chronic complications across the lifespan.[55] The homozygous HbSS genotype, commonly referred to as sickle cell anaemia (SCA), accounts for over 80% of cases of SCD.[55]

Overall, reliable disease frequency and epidemiology data are limited and vary by region. In the following sections, estimates from different data sources are shown, including sources that do not differentiate between SCD and SCA.

SI.2.1 Incidence

Globally, SCD incidence was estimated at approximately 112 per 100,000 live births, varying significantly by region (Table 5).[56]

Table 5 SCD Incidence at Birth, by Region

Region / Country	Source[a]	Affected births per 100,000
UK	Universal NBS programme for likely SCD[57]	50
Europe	Global meta-estimate[56]	43.12
North America	CDC[58, 59] Pilot study based on NBS Screening and known prevalent cases[60]	9 to 30
Middle East	Iraqi governorates from the Ministry of Planning[61]	13
Africa	Meta-estimate[56]	1125.49
Global	**Global meta-estimate[56]**	**111.91**

CDC: Centers for Disease Control and Prevention; NBS: newborn bloodspot screening; SCD: sickle cell disease; UK: United Kingdom
[a] Where data are available.

SI.2.2 Prevalence

Due to a lack of robust screening programmes and national registries, data on the global SCD prevalence are of variable quality and availability. Table 6 presents the available prevalence estimates by country. Overall, of the 20 to 25 million individuals with SCD worldwide, 12 to 15 million are estimated to be from sub-Saharan Africa, 5 to 10 million from India, and about 3 million distributed in different parts of the world.[62]

Table 6 Estimated Prevalence of Sickle Cell Disease, by Region

Region / Country	Source[a]	Estimated Prevalence
UK	National Haemoglobinopathy Registry, 2020[10]; Dormandy 2018[63]	12,803 to 14,000
Europe	Eurostat 2018[64, 65]	52,000
North America (US)	National Newborn Screening and Genetics Resource Center newborn bloodspot screening[66]	79,344 to 101,398
Middle East	TIF Global Thalassemia Review 2021[16] Iraqi governorates from the ministry of planning[61] National register, 1995[19, 67]	126,000+
Asia (India)	Aliyu 2008[62]	5 to 10 million
Africa	Aliyu 2008[62]	12 to 15 million
Global	**Aliyu 2008[62]**	**20 to 25 million**

SCD: sickle cell disease; TIF: Thalassemia International Federation; UK: United Kingdom; US: United States
[a] Where data are available.

SI.2.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Risk Factors for the disease

SCD is a genetic disease, therefore discussion of risk factors is not applicable.

Age at diagnosis

Although SCD is present at birth, the onset of clinical symptoms is delayed until approximately 6 months of age when HbF is rapidly replaced by adult HbS.[68] In industrialised countries, newborn screening has been the standard since 1978[69] leading to diagnosis within the first days of life. However, in most developing countries an absence of routine screening programmes has led to delayed diagnosis.[68, 70]

Age distribution among prevalent patients

In a cohort study using US Medicaid claims from 2000 to 2013 and including 44,033 beneficiaries with an SCD diagnosis, the mean age of patients was 15.7 years (66% of beneficiaries were ≤18 years of age).[71]

Sex

SCD is passed on to offspring through autosomal recessive inheritance. Most studies have demonstrated that the incidence of SCD among males and females is approximately equivalent, and there is no evidence to suggest that either sex is at higher risk for acquiring the disease. In the same US Medicaid study, 47% of the 44,033 beneficiaries with SCD were male.[71]

Race / Ethnic Origin

Cases of SCD have been observed in nearly every racial and ethnic group, but the disease occurs at disproportionately higher rates among individuals of African descent and then, to a lesser extent, among individuals of Middle Eastern, Mediterranean, Indian, and Asian descent.

Based on data from the USA New York State newborn screening programme for the years 2000 to 2008, newborns of non-Hispanic black mothers accounted for 86% of SCD cases, newborns of Hispanic mothers accounted for 12% of the cases, and newborns of

non-Hispanic white mothers accounted for <2% of the cases.[72] In the USA Medicaid study, 82% were African American, 3% were white, 5% were Hispanic, and 10% were other races.[71]

SI.2.4 Main Existing Treatment Options

The main existing treatment options for SCD are primarily directed at preventing complications of the disease and are not curative; these include pain management with opioids, chronic blood transfusions, hydroxyurea and other medications. These non-curative treatment options and associated risks are summarised in Table 7.

Table 7 Main Existing Treatments in Patients with Sickle Cell Disease

Treatment Options	Risks
Opioid analgesics	
• Analgesics for controlling severe pain, both acute and chronic, associated with VOC events • In a US Medicaid population of 44,033 beneficiaries with SCD diagnosis from 2000 to 2013, 40% were recorded to be using opioids at cohort entry.[71]	• Tolerance • Overdose • Dependence, with withdrawal symptoms upon discontinuation
Blood Transfusion	
• Blood transfusion therapy increases patient oxygen carrying capacity and alleviates symptoms associated with SCA. • Blood transfusions are typically indicated for SCA patients experiencing acute conditions, such as severe ACS, acute splenic sequestration with severe anaemia, stroke, etc.[73]	• Transfusion-related complications include transfusion-transmitted infections (in the US, largely due to transfusions given before 1990) and organ damage due to iron overload (e.g., heart disease, liver disease, endocrinopathies). • Organ damage due to iron build up leads to additional complications such as abdominal pain, weakness, fatigue, and joint pain.[74] • RBC alloimmunisation is a continuing, clinically significant risk among individuals receiving regular blood transfusions.[30]
Hydroxyurea/Hydroxycarbamide	
• Hydroxyurea ameliorates VOC and ACS in pediatric and adult SCA patients by increasing HbF. • In a US Medicaid population of 44,033 beneficiaries with SCD diagnosis from 2000 to 2013, only 12% were recorded to be using hydroxyurea at cohort entry.[71]	• Myelosuppression, a decrease in bone marrow leading to reduced blood cell production, is a common and serious side effect of cytotoxic hydroxyurea.[75] Common resulting toxicities include neutropenia, reticulocytopenia, and anaemia. • Other AEs include thrombocytopenia, ALT elevation, pain, headache, bleeding, gastrointestinal disturbances, unexplained fever, and minor infections.[75]
Oxbryta® (voxelotor)[76]	
• An HbS polymerisation inhibitor, which works by helping to prevent the process that causes RBCs to sickle	• Serious hypersensitivity reactions after administration of OXBRYTA have occurred in <1% of patients treated
Adakveo® (crizanlizumab)[a,77]	
• An anti-P-selectin antibody that inhibits interactions between endothelial cells, RBCs, platelets, and WBCs and reduces pain and inflammation associated with blood flow blockage.	• In the SUSTAIN clinical trial, infusion-related reactions (defined as occurring within 24 hours of infusion) were observed in 2 (3%) patients treated with ADAKVEO 5 mg/kg.

ACS: acute chest syndrome; ALT: alanine aminotransferase; EU: European Union; HbF: foetal haemoglobin; HbS: sickle haemoglobin; RBC: red blood cell; SCA: sickle cell anaemia; SCD: sickle cell disease; US: United States; VOC: vaso-occlusive crisis; WBC: white blood cell

[a] Adakveo (crizanlizumab) has been withdrawn from use in the EU.

Allogeneic HSCT is a potentially curative option for SCD. However, the availability of HSCT is generally limited to patients who have a matched stem cell donor (approximately 25% of eligible patients). Approximately 200 transplants for SCD are reported to the EBMT Patient Registry annually[33], whilst about 150 transplants for SCD are reported in the US every year.[34] Although transplantation provides relief from vaso-occlusive crises, the procedure is associated with significant risks (e.g., graft versus-host disease), as discussed in Section SI.3.1.

SI.2.5 Natural History of the Indicated Condition in the Untreated Population

Mortality

In the Jamaican Cohort Study of SCD (homozygous SS disease) with enrollment from 1973 to 1981 and follow up through 2016, Kaplan-Meier median survival for the whole cohort was estimated to be 42.3 years.[78] Similarly, in the Cooperative Study of Sickle Cell Disease (CSSCD) from 1979 to 1999, the median survival by sex was estimated at 42 years for males and 48 years for females.[79]

The increasing availability of newborn screening, immunisations, antibiotic prophylaxis and innovative therapies has reduced SCD mortality in industrialised countries over the past 4 decades. In a cohort study of 44,033 US Medicaid beneficiaries with SCD (2000 to 2013), the mortality rate was estimated at 1.4 per 100 PY.[71] The cumulative incidence of death evaluated over a maximum follow-up of 13 years showed an increase with age; the cumulative incidence of death by age was:

- 1.7% in patients <1 year of age;
- 1.3% in patients 2 to 6 years of age;
- 4.9% in patients 7 to 12 years of age;
- 15.0% in patients 13 to 18 years of age;
- 27.3% in patients 19 to 35 years of age; and
- 45.4% in patients >35 years of age.

In an analysis of 16,654 sickle cell-related deaths in US National Center of Health Statistics for the period 1979 to 2005, the causes of death were recorded as: SCD or sickle cell-related complications (65%), infection (6%), non-ischaemic heart disease (4%), ischaemic heart disease (3%), stroke (3%), and liver disease, accidental, lung disease (not pulmonary hypertension), renal disease, pulmonary hypertension, solid tumor, and pulmonary embolism (2% each).[80] The most common causes of death in the hydroxyurea-naïve population were acute chest syndrome (ACS) and sepsis.[78, 80] As individuals with SCD are living longer, mortality from chronic conditions such as renal failure is becoming more common.[81]

Morbidity

SCD is associated with numerous complications and comorbidities, including vaso-occlusive crisis (VOC), ACS, stroke, cardiac disease, pulmonary hypertension, chronic pulmonary disease, renal disease, bone disease, liver disease, and malignancies. Complications of SCD are discussed in more detail in Section SI.2.6.

SI.2.6 Important Complications and Comorbidities

This section describes both disease-related and treatment-related complications associated with SCD.

SI.2.6.1 Vaso-Occlusive Crises

Pain is the most frequent clinical problem in patients with SCD and the frequency of acute episodes of pain or VOC is traditionally used to define SCD severity.[82] Definitions of VOC vary across studies, but criteria typically depend on the level of clinical care needed (e.g., requiring hospitalisation, emergency care, or clinic visit; requiring treatment with narcotic pain medications).[71, 83, 84] Of note, the true burden of VOC pain is likely underestimated because many adults with SCD who have pain episodes do not seek urgent medical attention.[82, 85]

In a large cohort study of USA Medicaid beneficiaries with SCD (N=44,033; 2000 to 2013), VOC episodes were defined as pain requiring an emergency visit or hospitalisation. The overall average rate (95% CI) of VOC episodes in this study was 3.69 (3.68 to 3.70) per person per year.[71] The rate was substantially higher among patients 19 to 35 years of age and among patients with a higher baseline frequency of VOC (Table 8).

Table 8 VOC Rate Among US Medicaid Beneficiaries With SCD, by Age and Baseline VOC Frequency (2000 to 2013)

	VOC Episodes per Patient per Year (95% CI)		
Age (Years) at Cohort Entry	**<2 VOC Episodes per Year at Baseline**	**≥2 to ≤4 VOC Episodes per Year at Baseline**	**≥5 VOC Episodes per Year at Baseline**
<1	1.01 (0.99-1.03)	1.57 (1.54-1.6)	2.59 (2.48-2.72)
≥2 to ≤6	0.91 (0.9-0.92)	1.64 (1.62-1.67)	2.73 (2.66-2.81)
≥7 to ≤12	1.68 (1.67-1.7)	2.95 (2.92-2.98)	5.69 (5.59-5.78)
≥13 to ≤18	3.41 (3.38-3.44)	5.21 (5.16-5.25)	10.94 (10.83-11.04)
≥19 to ≤35	3.00 (2.97-3.03)	4.70 (4.66-4.73)	13.14 (13.08-13.20)
>35	1.58 (1.55-1.61)	3.15 (3.11-3.20)	11.25 (11.15-11.34)

Source: Desai[71]
CI: confidence interval; SCD: sickle cell disease; US: United States; VOC: vaso-occlusive crisis

SI.2.6.2 Acute Chest Syndrome

ACS is the second most common cause of hospitalisation in patients with SCD.[86-89] ACS is generally defined as a new radiodensity on chest radiograph accompanied by fever and/or respiratory symptoms.[90]

In the CSSCD (1979 to 1999), the overall incidence of ACS hospitalisations in SCD patients with the HbSS genotype was 12.8 per 100 PY. The incidence was highest for patients ≥2 to 4 years of age (25 per 100 PY), and decreased in adults >20 years of age (9 per 100 PY).[88] In a study of 1,056 patients with SCA (HbSS genotype) from a single USA medical centre who were observed for more than 4 decades (1959 to 2003), the incidence of ACS was estimated at 14 per 100 PY.[91] It is estimated that half of all individuals with SCD will experience at least one ACS episode.[92]

SI.2.6.3 Stroke

Neurologic complications are a major cause of morbidity and mortality in SCD and individuals with SCD are especially at risk of ischaemic and haemorrhagic stroke. The pathophysiology of stroke in SCD patients differs from that of the general population; specifically, vessel occlusion, binding of sickled cells to the endothelium, and increased hypercoagulability associated with SCD also increase risk for stroke.[93]

The incidence of first stroke in individuals with SCD varies with the genotype, patient age, and comorbidities. Without intervention, 11% of patients with SCD are estimated to have clinically apparent strokes by 20 years of age and 24% of patients by 45 years of age, along with a high risk of subsequent stroke.[94]

SI.2.6.4 Cardiac Disease

Patients with SCD lack sufficient healthy RBCs to transport adequate oxygen to tissues in the body. To protect against hypoxia, the decreased oxygen-carrying capacity of sickle cells must be compensated for with increased cardiac output. Elevated cardiac output leads to overexertion of the left ventricle (LV) and eventually, diastolic dysfunction.[95] The prevalence of diastolic dysfunction in SCD patients is estimated between 10% and 22%, depending on diagnostic tool.[96, 97]

In an autopsy study of 52 patients (25 adults, 27 children) with SCA, LV dilation was found in 44% of adults and 30% of children and LV hypertrophy was found in 36% of adults and 22% of children.[98] Clinical evidence of congestive heart failure was found in 33% of patients. Only 12% of adults and 26% of children had no cardiac abnormalities identified.[98]

SI.2.6.5 Pulmonary Hypertension

Pulmonary hypertension is a serious complication diagnosed by right heart catheterisation in approximately 10% of adults with SCD.[99, 100] In addition, 30% to 40% of adults with SCD present with elevated (≥2.5 m/s) tricuspid regurgitant jet velocity, a surrogate marker for pulmonary hypertension.[99, 100]

SI.2.6.6 Chronic Pulmonary Disease

Asthma is a common feature of SCD among patients of all ages and may be related to genetic or environmental factors, or a consequence of the underlying haemolytic and inflammatory state in SCD patients.[101] The prevalence of asthma in both adults and adolescents with SCD ranges from 30% to 48%, compared to only 8.4% in the general US population.[102-104]

SI.2.6.7 Bone Disease

Low bone mineral density (BMD) is a common complication of SCD that leads to osteopenia and osteoporosis. The prevalence of low BMD among adults and children with SCD is estimated between 64% and 81.5%[105-108] and presents most frequently in the lumbar spine.[106, 109, 110] Osteopenia is reported in 31% to 57% of SCD patients, and osteoporosis in 24.5% to 40% of SCD patients.[106, 108]

Low BMD predisposes patients to fractures. In a multi-centre study of 268 young adults with SCD, lifetime prevalence of fractures was estimated at 28% to 32% among males and 16% to 17% among females.[111]

Avascular necrosis (AVN), or bone tissue death, results from inadequate blood supply and is a serious complication in patients with SCD. The prevalence and nature of necrosis for AVN varies by geographic region. In a small study of 27 patients with SCD from the UK, 41% of patients had AVN of at least 1 hip.[112] In a Nigerian study with 416 SCD patients, 15.9% of patients presented with clinical and radiologic features of AVN of the femoral head.[113] Among paediatric patients with SCA in Brazil, the prevalence of femoral AVN was estimated to be 39.4%.[114]

SI.2.6.8 Liver Disease

Acute hepatobiliary manifestations of SCD include acute hepatic crisis, intrahepatic cholestasis, and hepatic sequestration.[115] Acute hepatic crisis, characterised by jaundice, low grade fever, and right upper quadrant abdominal pain, is estimated to occur in about 10% of patients with SCA.[116, 117] Hepatic sequestration, characterised by acute liver enlargement, abdominal pain and anaemia due to vaso-occlusion, is rare and primarily documented in isolated case reports.[115]

Viral hepatitis may be present in patients with SCD, with patients who have a history of repeat blood transfusions being at an increased risk relative to the general population.[118,119] Elevated bilirubin is a common feature of SCD, even in the absence of clinically diagnosed liver disease. Mild elevations of bilirubin are observed in approximately 72% of patients with SCD.[120]

Cirrhosis may arise as a consequence of hypoxic injury from sickling, hepatitis, gallstones, iron overload, and/or alcohol abuse in patients with SCD.[121] The prevalence of cirrhosis among patients with SCD is estimated between 16% and 18%.[122, 123]

In severe cases of SCD, rapid haemolysis and continuous production of bilirubin can lead to the development of cholelithiasis. The estimated prevalence of cholelithiasis ranges from approximately 25% to 58% in patients with SCD.[124-126]

SI.2.6.9 Renal Disease

Given the high oxygen demands of the kidneys, a variety of structural and functional renal abnormalities are observed in patients with SCD.[127] Manifestations of sickle cell nephropathy include urinary concentrating defect, impaired renal acidification and potassium excretion, proteinuria, haematuria, and papillary necrosis, and impaired renal function.[128]

The prevalence of microalbuminuria (i.e., 30 to 300 mg/g) occurs in nearly 16% of children with SCD and in 33% of adults with SCD.[129]

Impaired renal function begins with hyperfiltration (increased glomerular filtration rate), which is a marker of renal response to early renal injury, which can then be followed by chronic renal failure and ultimately end-stage renal disease.[130] Approximately 5% of patients with SCA are estimated to develop renal failure, with the median age of disease onset being 23.1 years.[131]

SI.2.6.10 Malignancy

Population-based studies show that patients with SCD have higher risks of malignancy, including leukaemia, as compared to people with no SCD or to the general population.

A UK study of 7512 SCD patients and 118,821 controls who were hospitalised with minor medical and surgical conditions showed that SCD patients had a 2 times higher rate of any type of cancer and higher rate of specific cancer subtypes, including haematologic malignancies (3 times higher rate of lymphoid leukaemia and 10 times higher rate of myeloid leukaemia) (Table 9).[132]

Table 9 Increased Rate of Cancer in SCD Patients Relative to Controls in a UK Population-Based Study

Malignancy Type	Number of cancers in SCD patients (N=7512)	Rate Ratio (SCD vs controls)	95 % CI for Rate Ratio
All cancers	**142**	**2.1**	**1.7-2.5**
Hodgkin's lymphoma	8	3.7	1.5-8.4
Non-Hodgkin's lymphoma	13	2.6	1.3-4.8
Multiple myeloma	14	5.5	2.8-10.1
Lymphoid leukaemia	8	3.3	1.3-8.0
Myeloid leukaemia	14	10.0	4.6-21.5

Source: Seminog[132]
CI: confidence interval; SCD: sickle cell disease; UK: United Kingdom

An increased risk of haematologic malignancies (specifically, leukaemia) in SCD versus general population was also found in a USA California population-based analysis of 6423 SCD patients (Table 10).[133] The results are summarised in Table 11 and indicate that the rate of leukaemia is 2 times higher in SCD than general population. Notably, whilst the rate for haematologic malignancy was increased in SCD in these studies compared to general population, the absolute risk was relatively low.

Table 10 Increased Rate of Haematologic Tumors in SCD Patients Relative to General Population in US

Malignancy Type	Number of cancers in SCD patients (N=6423)	Standardised Incidence Ratio	95 % CI for Standardised Incidence Ratio
Haematologic tumors	31	1.7	1.2 to 2.4
Lymphoma	15	1.5	0.8 to 2.4
Leukaemia	12	2.3	1.2 to 4.1
Acute lymphocytic leukaemia	3	1.8	0.4 to 5.4
Chronic lymphocytic leukaemia	3	4.8	1.0 to 14.1
Acute myeloid leukemia	6	3.6	1.3 to 7.8

Source: Brunson[133]
CI: confidence interval; SCD: sickle cell disease; US: United States

In addition to an increased risk of cancer in the SCD population relative to general population, there are suggestions in the literature that SCD patients undergoing curative therapies for SCD may be at increased risk of leukaemia.[134] Studies reporting on risk of leukaemia or myelodysplastic syndrome (MDS) following various transplant-related conditioning regimens are summarised in Table 11. Overall, reported incidence of MDS or leukaemia varies across the studies from 0% to approximately 4%, the latter estimate being notably higher than in SCD patients without conditioning therapies. The variability may be due to the different types of conditioning therapies and conditioning regimens used across the studies.

Table 11 MDS or Leukaemia in SCD Patients With Curative Therapies

Source	Sample Size	Transplant Type	Conditioning	N (%) with MDS or leukaemia	Time to MDS or leukaemia
Ghannam[135]	76	HLA-matched sibling Haploidentical	Alemtuzumab, 300-400 cGy TBI, PT-Cy 0-100 mg/kg	3 (3.9%)	2 to 5 years
Jones[136]	47	Gene therapy	Busulfan	2 (4.3%)	3 to 5.5 years
Vermylen[137]	50	HLA-matched family member	Busulfan, Cy, ±r-ATG, ±TLI	1 (2%)	35 months
Bernaudin[138]	234	HLA-matched sibling	Busulfan, Cy, r-ATG	0 (0%)	Not available
Eapen[139]	910	Mostly HLA-matched sibling	Mostly busulfan, Cy, r-ATG	5 (0.55%)	9 to 44 months

Source: Gondek[134]

cGy: centigray; Cy: cyclophosphamide; HLA: human leukocyte antigen; MDS: myelodysplastic syndrome; PT-Cy: post-transplant cyclophosphamide; r-ATG: rabbit-anti-thymocyte globulin; SCD: sickle cell disease; TBI: total body irradiation; TLI: total lymphoid irradiation

SI.2.6.11 Other Comorbidities

Other commonly reported SCD complications include leg ulcers (8% to 10% in the US)[129, 140, 141], venous thromboembolisms (25%) including pulmonary embolisms (13%)[142], ophthalmic complications[143], depression[144-147], and, in men, priapism (affects 40% males with SCD).[129, 140, 148, 149]

SI.3 Risks and Complications Associated with Stem Cell Transplantation

SI.3.1 General Risks of Stem Cell Transplantation

The overall disease or event-free survival for up to 5 years after HLA-matched sibling allogeneic HSCT is 82% to 86% for TDT[150, 151] and 89% to 97.8% for SCD.[138, 152, 153] The best outcomes are when allogeneic HSCT is performed HLA-matched sibling donors compared to alternative donor sources, and when transplant is performed at younger ages, before accumulating any thalassemia-related or SCD-related end-organ damage. However, HLA-matched sibling donors are only available in approximately 25% to 30% of patients with TDT and 18% of patients with SCD, thus highlighting the unmet need for effective therapies.[150, 151, 154, 155]

Significant risks associated with allogeneic HSCT for TDT and SCD include transplant-related mortality, graft failure, acute and chronic GVHD, and malignancy (Table 12).

Primary and secondary graft failure (or rejection) occur after allogeneic HSCT at a frequency of up to 9% to 14% in TDT and 7% to 9% in SCD.[151, 155-157] In both TDT and SCD, the majority of secondary graft failure (or rejection) events occur within the first year after transplant.[156, 151, 157]

Table 12 General Risks Associated with Myeloablative HLA-Matched Sibling Allogeneic HSCT in TDT and SCD

Risks	TDT	SCD
Death	4% to 20% at 2 years 8% (<6 years of age) to 37% (>16 to 25 years of age) at 5 years	0% to 19% at 4 and 5 years 0% (<5 years of age), 5% (<16 years of age) to 19% (>16 years of age)
Primary Graft Failure[a]	3% to 9%	2% to 7%
Secondary Graft Failure[b]	4% to 14%	2% to 9%
Acute GVHD	12% to 38% (Grade II-IV) 7% (Grade III-IV)	6% to 20% (Grade II-IV) 10% to 17.5% (Grade III-IV)
Chronic GVHD	8% to 13% (all grades) 5% (extensive)	14% to 18% (all grades) 3% to 5% (severe)
Infection[c]	Any infection: 70% Severe infection: 10% to 30% CMV reactivation: 15% to 40%	Bacteremia: 29% Severe infection: 10% CMV reactivation: 18% to 25%
Bleeding Events leading to death	1%	1% to 2%
Malignancy[d]	<1% to 1%	<1% to 1%

Sources: References[138, 150-153, 155, 157-163]

ANC: absolute neutrophil count; CIBMTR: Center for International Blood and Marrow Transplant Research; CMV: cytomegalovirus; EBMT: European Group for Blood and Marrow Transplantation; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; HSCT: haematopoietic stem cell transplantation; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

[a] Primary graft failure is defined as failure to reach the engraftment threshold by Day 28 post-transplant among patients receiving bone marrow-derived cells (EBMT, CIBMTR).

[b] Secondary graft failure is defined as a decrease in ANC to $<0.5\times10^9$ cells/L, after having achieved an ANC 0.5×10^9 cells/L or more; myeloid donor chimerism (<5%); or second transplant

[c] Post-transplant infections are often not reported in the literature unless severe or the cause of death.

[d] Malignancy risk is estimated at 5 years.

SI.3.2 Risks of Busulfan Conditioning

Myeloablation is a required step before exa-cel infusion in order to deplete endogenous HSCs from the bone marrow, thus allowing repopulation of HSCs containing the therapeutic edit. Busulfan has historically been a common agent used for myeloablative bone marrow conditioning and the risks for busulfan are well known and manageable.[164, 165]

Busulfan, an alkylating agent, has a toxicity profile that includes side effects of myeloablation, such as anaemia, neutropenia, and thrombocytopenia, which can lead to serious infections and increase the risk for bleeding complications.[166] Veno-occlusive liver disease (VOD) is a major complication of busulfan treatment, with a reported incidence between 3.9% to 15.4%; VOD events with busulfan occurred more frequently in the paediatric population.

The risk of malignancy exists with busulfan treatment; the International Agency for Research on Cancer classified busulfan as a human carcinogen and the WHO concluded that there is a causal relationship between busulfan exposure and subsequent development of a cancer. Busulfan has shown teratogenic properties in animal studies and use of busulfan is contraindicated during pregnancy; effective contraception use is required during treatment. There is also a risk of irreversible infertility with busulfan conditioning and fertility preservation options should be considered.[166]

SI.3.3 Neutrophil and Platelet Engraftment

During bone marrow repopulation, patients may be at increased risk of various cell-line specific complications.

Neutropenia following myeloablative therapy is associated with increased risk of infection due to viral, bacterial and/or fungal pathogens as well as neutropenic fever in the absence of identifiable infection. These events are considered common after HSCT, particularly during the period prior to neutrophil engraftment; prophylactic anti-infective agents and clinical standard of care aid in risk management.[167-170]

Thrombocytopenia following myeloablative conditioning is a risk factor for bleeding-related complications. Bleeding events may take the form of major haemorrhages (e.g., cystitis, gastrointestinal, diffuse alveolar, or central nervous system haemorrhages), or may only be observed through occult findings. Up to 30% of patients may experience a bleeding event prior to platelet engraftment, with prolonged or severe thrombocytopenia associated with the highest risk. Risks associated the pre-engraftment thrombocytopenia may be managed by routine administration of platelet transfusions.[171]

Times to neutrophil and platelet engraftment in TDT and SCD patients receiving autologous gene therapy or allogeneic HSCT are presented in Table 13.

Table 13 Time to Engraftment in HSCT

	TDT							SCD			TDT, SCD	
	Auto-GT	Allo-HSCT						Auto-GT	Allo-HSCT		Allo-HSCT	
Engraftment	Zynteglo USPI [172,a]	[redacted]	Bernado [174,c]	Sellanthamby [175,d]	Anurathapan [176,e]	Sun [177,f]	Ghavamzadeh [178,g]	Kanter [179,h]	[redacted]	Gluckman [152,j]	Locatelli [180,k]	King [181,l]
	N=41		N=60	N=102	N=83	N=48	N=96	N=35		N=1000	N=389	N=52
Neutrophil												
N1	41		59	102	83	48	96	35		1000	389	52
n	41		59	96	81	48	93	35		NR	360	51
% Engraft.	100%		100%	94%	97.6%	100%	96.9%	100%		98% D60	92% (±1) D60	98.1%
Time, days												
Median	26		20	16	14	13	19	20		19	19	13
Min, Max	13, 39		11, 30	8, 33	11, 20	10, 23	8, 160	12, 35		NR	8, 56	5, 21
Platelet												
N1	41		59	102	83	48	96	35		1000	389	52
n	41		59	91	81	48	93	35		NR	NR	51
% Engraft.	100%		100%	89%	97.6%	100%	96.9%	100%		96% M6	85% (±5) D180	98.1%
Time, days												
Median	46		20	28	30	12	26	36		25	25	25.9
Min, Max	20, 94		11, 36	13, 154	20, 45	8, 31	12, 210	18, 136		NR	NR	8, 120

N: Number of patients in study; N1: Number of patients with evaluable engraftment; n: number of patients who achieved engraftment; %: n/N1 (unless otherwise reported)
Allo: allogeneic; Auto: autologous; [redacted] GT: gene therapy; HSCT: haematopoietic stem cell transplant; NR: not reported; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia; USPI: United States Prescribing Information

Table 13 Time to Engraftment in HSCT

Notes: Populations receiving allogeneic transplants for SCD or TDT are primarily adolescent/pediatric (i.e., <18 years of age).

[a] Zynteglo (betibeglogene autotemcel) USPI: auto-HSCT GT with bone marrow. Platelet engraftment threshold >20×10^6/L for 3 days.

[b] [redacted]

[c] Bernado et al. allo-HSCT with bone marrow, peripheral blood, or umbilical cord blood. Platelet engraftment threshold ≥20×10^6/L once unsupported.

[d] Sellanthamby et al. allo-HSCT, bone marrow anticipated (not specified). Platelet engraftment threshold >20×10^6/L for 2 days.

[e] Anurathapan et al. allo-HSCT with peripheral blood. Platelet engraftment threshold ≥20×10^6/L (not otherwise specified).

[f] Sun et al. allo-HSCT with peripheral blood. Platelet engraftment threshold >20×10^6/L for 7 days.

[g] Ghavamzadeh et al. subset of patients who had allo-HSCT with bone marrow cells. Platelet engraftment threshold >20×10^6/L for 3 days.

[h] Kanter et al. auto-HSCT GT (lovotibeglogene autotemcel) with bone marrow. Platelet engraftment threshold ≥50×10^6/L for 3 days.

[i] [redacted]

[j] Gluckman et al. allo-HSCT with bone marrow, peripheral blood, or umbilical cord blood cells. Platelet engraftment threshold >20×10^6/L for 7 days.

[k] Locatelli et al. allo-HSCT with bone marrow or umbilical cord blood cells. Platelet engraftment threshold >50×10^6/L for 7 days. SCD cohort likely included in Gluckman (2017) and should not be considered a separate, unique cohort.

[l] King et al. allo-HSCT with bone marrow and/or umbilical cord blood. Platelet engraftment threshold ≥50×10^6/L for 7 days.

SII Nonclinical Part of the Safety Specification

Exa-cel has been studied in a variety of nonclinical studies to support clinical development and marketing authorisation as a treatment for patients with SCD and TDT (Module 2.6.2, Module 2.6.4, Module 2.6.6, and Module 2.4). These studies include specialised genotoxicity studies evaluating on-target editing as well as the potential for off-target editing and chromosomal aberrations; immunogenicity; pharmacokinetics (biodistribution and persistence); and a combined toxicity and tumorigenicity assessment (Table 14).

Overall, results from the nonclinical safety assessments demonstrate that exa-cel: 1) has a low risk for off-target editing, 2) has a low risk for inducing an immune response, and 3) resulted in no adverse findings, tumorigenicity, or unwanted biodistribution to non-target tissues in NOD/SCID/IL2Rγnull mice at a dose that was approximately 11× the minimum clinical dose evaluated.

Table 14 Nonclinical Studies in Exa-cel Development Programme

Study Type	Study cell/species	Findings	Relevance to use in Humans
Specialised Genotoxicity			
Off-target: Hybrid capture (deep sequencing) Module 2.6.6/ Section 4.1	$CD34^+$ hHSPCs from 4 healthy donors (in vitro)	• No detectable off-target editing, based on a frequency difference threshold of ≥1% above matched untreated control.	• Low risk for off-target editing.
Off-target: Hybrid capture (ultra-deep sequencing) Module 2.6.6/ Section 4.2	$CD34^+$ hHSPCs from 4 healthy donors (in vitro)	• No detectable off-target editing, based on a frequency difference threshold of ≥0.2% above matched untreated control.	• Low risk for off-target editing.
Off-target: Hybrid capture (ultra-deep sequencing) Module 2.6.6/ Section 4.3	$CD34^+$ hHSPCs from 3 SCD and 3 TDT patients (in vitro)	• No detectable off-target editing, based on a frequency difference threshold of ≥0.2% above matched untreated control.	• Risk for off-target editing with exa-cel is predicted to be low in the intended patient population.
Off-target: Hybrid capture (ultra-deep sequencing) Module 4.2.3.3.1	$CD34^+$ hHSPCs from 1 SCD and 2 TDT patients (in vitro)	• No detectable off-target editing, based on a frequency difference threshold of ≥0.2% above matched untreated control.	• Risk for off-target editing with exa-cel is predicted to be low in the intended patient population.
Extended On-target editing and translocations: Long-range PCR and hybrid capture Module 2.6.6/ Section 4.4.1	$CD34^+$ hHSPCs from healthy donors (in vitro)	• High rate of on-target indels formation, the majority of which were less than 30 base pairs in size. • Insertions detected in hybrid capture sequencing do not appear to arise from inter-chromosomal translocations.	• High rate of editing at the on-target site. • Low risk for translocations.
Karyotyping Module 2.6.6/ Section 4.5	$CD34^+$ hHSPCs from 3 healthy donors (in vitro)	• No detectable chromosomal aberrations greater than background.	• Low risk for translocations and large chromosomal abnormalities.

Table 14 Nonclinical Studies in Exa-cel Development Programme

Study Type	Study cell/species	Findings	Relevance to use in Humans
Immunogenicity			
Innate immune response Module 2.6.6/ Section 8.1.1	$CD34^+$ hHSPCs from 2 healthy donors (in vitro)	• SPY101-RNP did not results in increased expression of genes indicating a type 1 IFN response in CD34+ hHSPCs.	• Low risk for inducing an innate immune response.
Biodistribution and Persistence			
Pivotal 20-week biodistribution and persistence study Module 2.6.4/ Section 4.1	IV injection of $CD34^+$ hHSPCs to irradiated NSG mice	• Engraftment and persistence of exa-cel confirmed in haematopoietic tissues (e.g., bone marrow) up to 20 weeks after infusion. • No evidence of aberrant migration, accumulation, or persistence in non-target tissues, including in the reproductive organs	• Engraftment and durability of edited cells is expected. • Editing of hHSPCs with exa-cel does not appear to affect hHSPCs tissue distribution or persistence.
Toxicity and Carcinogenicity			
Pivotal 20-week toxicity and tumorigenicity study Module 2.6.6/ Section 5.2	IV injection of $CD34^+$ hHSPCs to irradiated NSG mice	• There were no adverse findings or evidence of tumorigenicity.	• Risk of edited CD34+ hHSPCs leading to adverse toxicity or neoplasia is low.

exa-cel: exagamglogene autotemcel; hHSPCs: human haematopoietic stem and progenitor cells; IV: intravenous; NSG: NOD/SCID/IL2Rγnull; PCR: polymerase chain reaction; SPY101 RNP: gRNA Cas9 ribonucleoprotein

SIII Clinical Trial Exposure

Cumulatively, as of the data cut-off dates on 16 April 2023 for TDT and SCD, a total of 97 subjects 12 to 35 years of age were treated with exa-cel (Table 15). The median exa-cel dose was 8.0×10^6 (range: 3.0×10^6 to 19.7×10^6) $CD34^+$ cells/kg in subjects with TDT and 4.0×10^6 (range: 2.9×10^6 to 14.4×10^6) $CD34^+$ cells/kg in subjects with SCD. Follow-up duration after exa-cel infusion (from Study 111 or 121 through Study 131) included:

- 54 subjects with TDT followed for a median (max) of 22.8 (51.1) months, corresponding to 1.9 (4.3) years; and
- 43 subjects with SCD followed for a median (max) of 17.5 (46.2) months, corresponding to 1.5 (3.8) years.

Across both indications, this corresponds to a total of 167.0 patient-years of exposure after infusion of exa-cel.

Cumulative subject exposure by age, sex, race, and region are provided in Table 16. Overall, of the 97 subjects with TDT or SCD treated with exa-cel, the majority were aged ≥18 years (68.0%) and there was [redacted] proportion of [redacted] and [redacted] subjects. In subjects with TDT, there was [redacted] proportion of subjects who were [redacted], and [redacted] proportion of subjects located at sites in Europe [redacted] and North America [redacted]. In subjects with SCD, the [redacted] of subjects were [redacted] and [redacted] subjects were from sites located in North America [redacted]

Table 15 Cumulative Subject Exposure From Clinical Studies in the Exa-cel Development Programme

Treatment	Number of Subjects		
	TDT (Study 111 + Study 131)	SCD (Study 121 + Study 131)	Total TDT + SCD through Study 131
Number of subjects who initiated mobilisation	59	58	117
Number of subjects who initiated conditioning	54	43	97
Number of Subjects Infused with Exa-cel (n)	54	43	97
Number of subjects who completed Study 111 or 121 and enrolled in Study 131	23	13	36
Exposure after exa-cel infusion including Study 131			
n	54	43	97
Patient-years	100.5	66.5	167.0
Patient-months	1205.9	797.9	2003.8
Follow-up duration after exa-cel infusion (years)			
Mean (SD)	1.9 (0.88)	1.5 (0.83)	--
Median	1.9	1.5	--
Min, Max	0.2, 4.3	0.1, 3.8	0.1, 4.3
Follow-up duration after exa-cel infusion (months)			
Mean (SD)	22.3 (10.51)	18.6 (9.99)	--
Median	22.8	17.5	--
Min, Max	2.1, 51.1	1.2, 46.2	1.2, 51.1
Follow-up duration after exa-cel infusion by interval, n (%)			
≤3 months	2 (3.7)	2 (4.7)	4 (4.1)
>3 to ≤6 months	4 (7.4)	2 (4.7)	6 (6.2)
>6 to ≤12 months	4 (7.4)	8 (18.6)	12 (12.4)
>12 to ≤24 months	20 (37.0)	16 (37.2)	36 (37.1)
>24 to ≤36 months	19 (35.2)	13 (30.2)	32 (33.0)
>36 months	5 (9.3)	2 (4.7)	7 (7.2)
Exa-cel Dose (CD34+ cells $\times 10^6$/kg)			
Mean (SD)	8.4 (4.26)	4.7 (2.47)	--
Median	8.0	4.0	--
Min, Max	3.0, 19.7	2.9[a], 14.4	2.9[a], 19.7

Sources: 111-131 Table 14.1.1a (t-ds-disp-111)/14.1.10.1a (t-ex-ctxfu-fas-111); 111: Table 14.1.10.1 (t-ex-ctxdose); 121-131: Tables 14.1.1b (t-ds-disp-121)/14.1.10.1b (t-ex-ctxfu-fas-121); 121: Table 14.1.10.1 (t-ex-ctxdose)

exa-cel: exagamglogene autotemcel; SCD: sickle cell disease; SD: standard deviation; TDT: transfusion-dependent β-thalassemia

Notes:

- All data presented are based on the available data in the clinical database as of 16 April 2023 for subjects with TDT (Studies 111 and 131) and SCD (Studies 121 and 131). All 3 studies were ongoing. A subject may be counted under more than 1 dosing category based on status at time of data cut.
- Exposure after exa-cel infusion (patient-months/patient-years) = Sum of follow-up duration (months/years) after exa-cel infusion.
- Follow-up duration (month) after exa-cel infusion = (Data cut-off date or end of study date, whichever is earlier - exa-cel infusion date + 1)/30
- Follow-up duration (year) after exa-cel infusion = Follow-up duration after exa-cel infusion (months)/12

[a] Based on post-infusion adjustments to the density coefficient of the final formulation medium used for exa-cel drug product calculation, the drug product was recalculated and it was determined that the recalculated dose for 3 subjects with SCD was lower than the protocol specified minimum dose of 3×10^6 $CD34^+$ cells/kg (subjects received 2.9×10^6 $CD34^+$ cells/kg). All subjects were infused per protocol.

Table 16 Cumulative Subject Exposure After Exa-cel From Clinical Studies in the Development Programme, by Age Group, Sex, Racial Group, and Region

	TDT (Study 111 + Study 131)		SCD (Study 121 + Study 131)		Total TDT + SCD through Study 131	
	Number of Subjects n/N (%)	Exposure after Exa-cel (PY)	Number of Subjects n/N (%)	Exposure after Exa-cel (PY)	Number of Subjects n/N (%)	Exposure after Exa-cel (PY)
Subjects infused with exa-cel	54	100.5	43	66.5	97	167.0
Age Group (years)						
>12 to <18	19 (35.2)	28.3	12 (27.9)	12.5	31 (32.0)	40.8
≥18 to ≤35	35 (64.8)	72.2	31 (72.1)	54.0	66 (68.0)	126.2
Sex, n	[redacted]					
Race, n	[redacted]					
Region, n						
Europe	[redacted]					
North America						

Sources: 111-131 Table 14.1.3.1a (t-dm-demo-111)/14.1.10.1a (t-ex-ctxfu-fas-111)/14.1.11a (t-ah-ex-ctxfu-sub1-111); 121-131: Tables 14.1.3.1b (t-dm-demo-121)/14.1.10.1b (t-ex-ctxfu-fas-121)/14.1.11b (t-ah-ex-ctxfu-sub1-121); 121: Listing 16.2.1.1 (l-ds-disp)

N: number of subjects infused with exa-cel; PY: patient-years; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia.

Notes:

- All data presented are based on the available data in the clinical database as of 16 April 2023 for subjects with TDT (Studies 111 and 131) and SCD (Studies 121 and 131). All 3 studies were ongoing. Demographic data are based on information provided when subject signed the informed consent to enter either Study 111 or Study 121.
- Exposure after exa-cel infusion (patient-years) = Sum of follow-up duration (years) after exa-cel infusion.

[a] [redacted]

SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme	
TDT and SCD	
Patients >35 years of age	
Reason for exclusion	Historically, few adults with TDT or SCD older than 35 years of age have undergone allogeneic HSCT. Therefore, patients over 35 years of age were excluded from clinical studies prior to the benefit/risk of exa-cel being established. There are no unique or specific reasons why patients >35 years of age who are otherwise eligible for the HSCT procedure and meet guidelines established for adequate organ function could not receive exa-cel; therefore, it is not expected that age >35 years would be a limitation for exa-cel treatment.
Is it to be considered missing information?	Yes
Rationale	Treatment of exa-cel in patients >35 years of age will be evaluated through post-authorisation surveillance.
Prior treatment with allogeneic HSCT or gene therapy/editing product	
Reason for exclusion	Subjects who had previous treatment with allogeneic HSCT or gene therapy/editing product were excluded from studies as this history could confound the results of the study and might also confound the benefit-risk assessment.
Is it to be considered missing information?	No
Rationale	Treatment with exa-cel has not been studied in patients who received a prior allogeneic or autologous HSCT and use of exa-cel is not recommended in these patients.
Pregnancy and lactation	
Reason for exclusion	Pregnant and lactating women were excluded from clinical studies due to known adverse effects of busulfan conditioning on foetal development.
Is it to be considered missing information?	Yes
Rationale	The outcomes of pregnancy and lactation in patients who received exa-cel therapy will be evaluated as missing information in post-authorisation surveillance.
History of a significant bleeding disorder	
Reason for exclusion	As a precautionary measure, subjects with a history of significant bleeding disorder at screening were excluded from clinical studies to reduce the risk of bleeding complications following myeloablation.
Is it to be considered missing information?	No
Rationale	The eligibility of patients for HSCT is determined by experienced transplant physicians based on standard of care, taking into account the patient's current and historical clinical status. Therefore, patients at higher risk are not expected to undergo exa-cel therapy.
Abnormal liver function or Advanced liver disease (e.g., hepatic cirrhosis)	
Reason for exclusion	Subjects with these medical conditions are at a higher risk for liver toxicity events (e.g., veno-occlusive liver disease) during busulfan conditioning and HSCT and were excluded from clinical studies as a precautionary measure.
Is it to be considered missing information?	No
Rationale	The safety profile of conditioning agents is well established and taken into consideration by experienced transplant physicians prior to determination of eligibility. Clinical studies did not demonstrate any meaningful changes in liver function tests or liver dysfunction associated with exa-cel therapy.

Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme	
Abnormal cardiac function	
Reason for exclusion	Subjects with abnormal cardiac function may be at a higher risk to develop cardiac dysfunction (e.g., tachyarrhythmias, hypertension or hypotension, and left ventricular dysfunction) during myeloablative conditioning and HSCT[182], and were excluded from clinical studies as a precautionary measure.
Is it to be considered missing information?	No
Rationale	The safety profile of conditioning agents is well established and taken into consideration by experienced transplant physicians prior to determination of eligibility. Whilst clinical studies did not demonstrate any cardiac dysfunction associated with exa-cel therapy, the SmPC describes that subjects who had severely elevated iron in the heart were excluded from Study 111.
Abnormal Renal Function	
Reason for exclusion	Dosing adjustment for busulfan may be needed in patients with renal dysfunction, which could impact conditioning effectiveness, as 30% is cleared by the kidney. The effects of renal dysfunction on intravenous busulfan disposition have not been assessed.
Is it to be considered missing information?	No
Rationale	The safety profile of conditioning agents is well established and taken into consideration by experienced transplant physicians prior to determination of eligibility. The autologous CRISPR-edited cells would be expected to have a similar therapeutic effect and safety profile in patients with abnormal function as compared to patients with normal organ function. Clinical studies did not demonstrate any meaningful changes in renal function tests or renal dysfunction associated with exa-cel therapy in patients with normal renal function.
Diminished respiratory capacity	
Reason for exclusion	Subjects with diminished respiratory capacity as demonstrated by DLco <50% of predicted value (corrected for haemoglobin and/or alveolar volume) may be at a higher risk of pulmonary toxicity during and after myeloablative conditioning and HSCT; therefore, these patients were excluded from clinical studies as a precautionary measure.
Is it to be considered missing information?	No
Rationale	The safety profile of conditioning agents is well established and taken into consideration by experienced transplant physicians prior to determination of eligibility. The autologous CRISPR-edited cells would be expected to have a similar therapeutic effect and safety profile in patients with diminished respiratory capacity as compared to patients with normal respiratory capacity. Clinical studies did not demonstrate any meaningful changes in vital signs or respiratory parameters associated with exa-cel therapy.
Patients with intolerance, contraindication, or known sensitivity to plerixafor or busulfan or prior anaphylactic reaction with excipients of CTX001 product (DMSO).	
Reason for exclusion	Subjects who are intolerant, contraindicated, or have a known severe hypersensitivity to products used in clinical studies were excluded as a precautionary measure.
Is it to be considered missing information?	No
Rationale	Hypersensitivity to the exa-cel active substance or to any of the excipients is a contraindication. The SmPC provides a warning to monitor for hypersensitivity reactions during and after infusion. Additionally, contraindications to mobilisation and myoablative conditional agents must be considered prior to treatment with exa-cel.

Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme	
SCD Only	
History of untreated Moyamoya disease or presence of Moyamoya disease at Screening that in the opinion of the investigator puts the subjects at the risk of bleeding.	
Reason for exclusion	Moyomoya is an abnormal vasculature phenomenon seen in patients with SCD and poses the risk for severe, life-threatening complications, such as haemorrhage and/or infarct, during the peri-transplant period.
Is it to be considered missing information?	No
Rationale	The eligibility of patients for HSCT is determined by experienced transplant physicians based on standard of care, taking into account the benefit/risk assessment. Therefore, patients at higher risk are not expected to undergo exa-cel therapy.

DLco: lung diffusing capacity for carbon monoxide; DMSO: dimethyl sulfoxide; HSCT: haematopoietic stem cell transplant; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

SIV.2 Limitations to Detect Adverse Drug Reactions in Clinical Trial Development Programme

The clinical development programme is unlikely to detect certain types of adverse reactions, such as rare adverse reactions or adverse reactions with a long latency.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Type of Special Population	Exposure
Patients who are pregnant or lactating	Pregnant and lactating patients were excluded from clinical studies due to known adverse effects of busulfan myeloablative conditioning on foetal development. No subject in a clinical study to date has become pregnant after myeloablative conditioning or exa-cel infusion. The outcomes of pregnancy and lactation in patients who received exa-cel infusion will be evaluated as missing information in post-authorisation surveillance.
Patients with hepatic impairment	Patients should be assessed for hepatic impairment to ensure HSCT is appropriate. Subjects with advanced liver disease were excluded from the pivotal Phase 1/2/3 studies in subjects 12 years of age and older (Study 111 in TDT and Study 121 in SCD). However, an assessment of subjects with any medical history within the SOC Hepatobiliary disorders identified 16 (29.6%) subjects with TDT and 22 (51.2%) subjects with SCD who were infused with exa-cel. Overall, the safety data in these 38 subjects were consistent with the safety data in other subjects treated with exa-cel.
Patients with renal impairment	Patients should be assessed for renal impairment to ensure HSCT is appropriate. Subjects with abnormal renal function at screening were excluded from the pivotal Phase 1/2/3 studies in subjects 12 years of age and older (Study 111 in TDT and Study 121 in SCD). However, an assessment of subjects with any medical history within the SOC Renal and urinary disorders identified 13 (24.1%) subjects with TDT and 12 (27.9%) subjects with SCD who were infused with exa-cel. Overall, the safety data in these 25 subjects were consistent with the safety data in other subjects treated with exa-cel.
Patients with cardiovascular impairment	Subjects with abnormal cardiac function at screening were excluded from the pivotal Phase 1/2/3 studies in subjects 12 years of age and older (Study 111 in TDT and Study 121 in SCD). However, an assessment of subjects with any medical history within the SOC Cardiac disorders identified 5 (9.3%) subjects with TDT and 11 (25.6%) subjects with SCD who were infused with exa-cel. Overall, the safety data in these 16 subjects were consistent with the safety data in other subjects treated with exa-cel.

Type of Special Population	Exposure
Population with relevant different ethnic origin	TDT is a disease occurring primarily in [redacted] populations and in Study 111 the [redacted] of subjects infused with exa-cel were [redacted] SCD is a disease occurring [redacted] in [redacted] population and in Study 121 the [redacted] of subjects treated with exa-cel were [redacted] Therefore, the populations studied in the clinical studies were racially and ethnically representative of the TDT and SCD populations in general.

exa-cel: exagamglogene autotemcel; SCD: sickle cell disease; SOC: system organ class; TDT: transfusion-dependent β-thalassemia

SV Post-authorisation Experience

Not applicable

SVI Additional EU Requirements for Safety Specification

Potential for Misuse for Illegal Purposes

Exa-cel therapy is a product on restricted prescription that is only provided by experienced transplant physicians. There is no potential for misuse or illegal use of exa-cel.

SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The adverse drug reactions (ADRs) are described in Section 4.8 (Undesirable Effects) of the EU Summary of Product Characteristics (SmPC) but are not considered to be important risks for exa-cel as these events are consistent with the known side effects of the HSCT procedure, for which the risk minimisation actions are part of standard of care for physicians with experience in HSCT and in the treatment of patients with β-hemoglobinopathies (see SmPC Section 4.2).

Overall, the ADRs are not expected to have a significant impact on the exa-cel benefit-risk profile and will be followed up via routine pharmacovigilance, including signal detection activities and adverse reaction reporting.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Descriptions of the initially proposed important identified risks, important potential risks, and missing information are provided herein; changes will be captured in Section SVII.2.

SVII.1.2.1 Important Identified Risk – Delayed platelet engraftment

Benefit-Risk Impact

In the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), median times to platelet engraftment after exa-cel infusion were comparatively longer than reported in allogeneic HSCT; however, the times were consistent with the median times reported in other genetic therapies involving HSCT. There was no association observed between bleeding adverse events (AEs) and time to platelet engraftment after exa-cel infusion. However, thrombocytopenia following myeloablative conditioning is a risk factor for serious bleeding-related complications, with the highest risk

occurring prior to platelet engraftment. As such, delayed platelet engraftment is considered an important identified risk.

SVII.1.2.2 Important Potential Risk – Neutrophil engraftment failure

Benefit-Risk Impact
Neutrophil engraftment failure is considered an important potential risk because of the possibility for neutrophil engraftment failure to be an outcome of any myeloablation and bone marrow transplantation. Failure to achieve neutrophil engraftment would require a subsequent HSCT procedure with unmodified rescue $CD34^+$ stem cells collected prior to conditioning, thereby negating beneficial effects of exa-cel gene therapy. However, in the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), there was no evidence of neutrophil engraftment failure after exa-cel infusion and this risk is considered potential.

SVII.1.2.3 Important Potential Risk – Gene editing-related oncogenesis

Benefit-Risk Impact
To date, there have been no reports of gene editing-related oncogenesis (e.g., myelodysplasia, leukaemia, or lymphoma due to treatment with exa-cel) in the clinical programme. However, gene editing-related oncogenesis is theoretically possible and is thus considered an important potential risk.

SVII.1.2.4 Missing Information – Long-term effects

Benefit-Risk Impact
As of April 2023 for pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), the maximum follow-up duration after exa-cel infusion was 51.1 months in subjects with TDT and 46.2 months in subjects with SCD, representing a cumulative total of 167 patient-years for both indications. Exa-cel therapy is intended to have life-long benefits by way of permanent and irreversible gene editing resulting in elevated hemoglobin F. Long-term effects of exa-cel therapy is considered missing information and further characterisation is needed.

SVII.1.2.5 Missing Information – Pregnancy and lactation

Benefit-Risk Impact
The effects of exa-cel on pregnancy and lactation in humans are not known as no clinical studies were conducted in these populations. Therefore, the safety outcomes of pregnancy and lactation in patients who received exa-cel therapy is considered missing information and further characterisation is needed.

SVII.1.2.6 Missing Information – Use in patients >35 years of age

Benefit-Risk Impact
Patients >35 years of age were not included in pivotal Phase 1/2/3 clinical studies in subjects with TDT (Study 111) or SCD (Study 121). Patients >35 years of age are eligible for exa-cel therapy in the post-authorisation setting if appropriate for HSCT; therefore, use in this age group is considered missing information and further characterisation is needed.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable in initial version of EU RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risk – Delayed platelet engraftment

Potential mechanisms
No mechanism was identified for delayed platelet engraftment in the exa-cel clinical programme as compared to allogeneic transplant literature.

Evidence source(s) and strength of evidence
In the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), median time to platelet engraftment after exa-cel infusion was comparatively longer than reported in allogeneic HSCT; however, the times were consistent with the median time reported in other genetic therapies involving HSCT. There was no association observed between bleeding AEs and time to platelet engraftment after exa-cel infusion. However, thrombocytopenia following myeloablative conditioning is a risk factor for serious bleeding-related complications, with the highest risk occurring prior to platelet engraftment. As such, delayed platelet engraftment is considered and important identified risk.

Characterisation of the risk
Platelet engraftment was defined as 3 consecutive platelet counts of $\geq 20 \times 10^9$/L in subjects with TDT and 3 consecutive measurements of platelet counts $\geq 50 \times 10^9$/L in subjects with SCD, obtained on 3 different days after exa-cel infusion, without administration of platelet transfusions for 7 days.

In the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age, the median (min, max) time to platelet engraftment after exa-cel infusion was 44 (20, 200) days in subjects with TDT (Study 111, N=53) and 35 (23, 126) days in subjects with SCD (Study 121, N=43). Platelet engraftment times were similar between adolescent subjects (12 to 17 years of age) and adult subjects (18 to 35 years of age). As of the data cut date, 53 of 54 subjects achieved platelet engraftment.

Overall, the median times to platelet engraftment after exa-cel infusion were comparatively longer than reported in allogeneic HSCT literature: median (range) of 12 to 30 [1, 330] days[173-178] in patients with TDT and 25 to 27 (1, 299) days[152, 173] in patients with SCD. However, these times were consistent with median times reported in other genetic therapies involving HSCT: median (range) of 46 (20, 94) days[172] in patients with TDT and 36 (18, 136) days[179] in patients with SCD.

Following platelet engraftment, platelet counts were generally maintained and improved over time. The median (min, max) time to first platelet count $\geq 100 \times 10^9$/L was 63 (22, 736) days in subjects with TDT (N=47) and 45.5 (26, 183) days in subjects with SCD (N=40).

The majority of bleeding events overall were non-serious, Grades 1 or 2 in severity, and not related to exa-cel. No subject in either study had a bleeding SAE associated with delayed platelet engraftment. Bleeding events that were Grades 3 or 4 in severity occurred at a similar incidence relative to the median time to platelet engraftment in each study:

- In subjects with TDT (Study 111), Grade 3 or 4 bleeding events occurred in 6 (23.1%) subjects who achieved platelet engraftment before the study median (<44 days) (N=26) and in 5 (18.5%) subjects who achieved platelet engraftment on or after the study median (≥44 days) (N=27).

- In subjects with SCD (Study 121), Grade 3 or 4 bleeding events occurred in 1 (4.8%) subject who achieved platelet engraftment before the study median (<35 days) (N=21) and in 2 (9.1%) subjects who achieved platelet engraftment on or after the study median (≥35 days) (N=22).

Overall, there was no association between bleeding events and times to platelet engraftment after exa-cel treatment in either study.

Risk factors and risk groups
Following infusion with exa-cel, subjects with TDT without a spleen (i.e., surgically splenectomised) had an earlier median time to platelet engraftment than subjects with an intact spleen. This finding is similar to data from allogeneic HSCT and other genetic therapies for β-thalassemia major.[172, 183]

Preventability
Platelet counts should be monitored and managed according to standard guidelines and medical judgement. Blood cell count determination and other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise.

Impact on the benefit-risk balance of the product
There is an increased risk for bleeding events following myeloablative conditioning, with the highest risk of bleeding after HSCT occurring before platelet engraftment.[184] However, all subjects engrafted after exa-cel infusion and no clinically relevant sequalae were observed in patients with longer platelet engraftment times. Patients will be monitored regularly by physicians familiar with the risks of HSCT. Therefore, this risk is not expected to significantly impact the benefit-risk balance.

Public health impact
Autologous HSCT with exa-cel is an individualised therapy and no public health impact is anticipated.

SVII.3.1.2 Important Potential Risk – Neutrophil engraftment failure

Potential mechanisms
Neutrophil engraftment failure is a possible outcome of any HSCT procedure.

Evidence source(s) and strength of evidence
Neutrophil engraftment failure is considered an important potential risk because of the possibility for neutrophil engraftment failure to be an outcome of any myeloablation and bone marrow transplantation. Failure to achieve neutrophil engraftment would require a subsequent HSCT procedure with unmodified rescue $CD34^+$ stem cells collected prior to conditioning, thereby negating beneficial effects of exa-cel gene therapy.

In the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), there was no evidence of neutrophil engraftment failure after exa-cel infusion; therefore, this risk is considered a potential risk.

Characterisation of the risk
Neutrophil engraftment failure was defined as not achieving neutrophil engraftment and requiring use of unmodified rescue $CD34^+$ stem cells.

In the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), all subjects achieved neutrophil engraftment without requiring the use of unmodified rescue $CD34^+$ stem cells.

Whilst all subjects achieved successful neutrophil engraftment after exa-cel infusion, neutrophil engraftment failure can occur in any patient who undergoes myeloablation and bone marrow transplantation; therefore, neutrophil engraftment failure is considered an important potential risk.

Risk factors and risk groups
As no subjects with TDT or SCD failed to achieve neutrophil engraftment following exa-cel infusion, no risk factors or risk groups were identified in the clinical programme.

Preventability
Patients should be monitored for absolute neutrophil counts and infections should be managed according to standard guidelines and medical judgement. Unmodified rescue $CD34^+$ stem cells should be collected prior to conditioning and administered in the event that neutrophil engraftment failure occurs.

Impact on the benefit-risk balance of the product
Failure to achieve neutrophil engraftment would require a subsequent HSCT procedure with unmodified rescue $CD34^+$ stem cells, thereby negating beneficial effects of exa-cel gene therapy. However, there has been no evidence of neutrophil engraftment failure following exa-cel infusion in any clinical study.

Public health impact
Autologous HSCT with exa-cel is an individualised therapy and no public health impact is anticipated.

SVII.3.1.3 Important Potential Risk – Gene editing-related oncogenesis

Potential mechanisms
There is a theoretical risk of oncogenesis after gene editing. A potential mechanism of this theoretical risk is off-target gene editing; however, exa-cel was designed to minimise off-target editing risk by choosing an ex vivo editing procedure that transiently exposes the cells to Cas9, selecting an on-target site with a sequence that is unique within the human genome, and using a highly specific guide RNA.

Evidence source(s) and strength of evidence
To date, there have been no reports of gene editing-related oncogenesis (e.g., myelodysplasia, leukaemia, or lymphoma due to treatment with exa-cel) in the clinical programme. However, gene editing-related oncogenesis is theoretically possible; therefore, this risk is considered potential.

Characterisation of the risk
Three comprehensive non-clinical off-target assessments found high rates of editing at the on-target *BCL11A* site and no off-target editing. These assessments were performed in 14 individuals of diverse ancestry, 3 of whom had SCD and 3 with TDT, and spanned thousands of candidate sites nominated by either computational homology or experimental methods (using GUIDE-Seq) taking into account genetic variation. The nominated sites were then analyzed by deep hybrid capture sequencing, which confirmed that there are no off-target sites. To date, there have been no reports of gene editing-related oncogenesis in follow-up of up to 4 years after exa-cel infusion, and no findings of off-target editing in clinical samples tested.

Risk factors and risk groups
To date, there have been no reports of gene editing-related oncogenesis; therefore, no risk factors or risk groups were identified.

Preventability
Patients should be monitored annually (including complete blood count) and be managed according to standard guidelines and medical judgement.

Impact on the benefit-risk balance of the product
Gene editing-related oncogenesis may result in myelodysplasia, leukaemia, or lymphoma, for which treatment may include bone marrow transplantation, which incurs additional risk, e.g., from additional conditioning.

Public health impact
Autologous HSCT with exa-cel is an individualised therapy and no public health impact is anticipated.

SVII.3.2 Presentation of the Missing Information

SVII.3.2.1 Missing Information – Long-term effects

Evidence source
As of April 2023 for pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) or SCD (Study 121), the maximum follow-up duration after exa-cel infusion was 51.1 months in subjects with TDT and 46.2 months in subjects with SCD, representing a cumulative total of 167 patient-years for both indications. Exa-cel therapy is intended to have life-long benefits by way of permanent and irreversible gene editing. Therefore, long-term effects of exa-cel therapy is considered missing information and further characterisation is needed.

Population in need of further characterisation
Long-term safety and efficacy of exa-cel (including 15 years after exa-cel infusion) remains under ongoing evaluation in clinical and post-authorisation studies and routine surveillance.

SVII.3.2.2 Missing Information – Pregnancy and lactation

Evidence source
The effects of exa-cel on pregnancy and lactation in humans are not known as no clinical studies were conducted in these populations. No pregnancies or breastfeeding after the start of myeloablation or exa-cel infusion have been reported in the clinical programme. Therefore, the safety outcomes of pregnancy and lactation in patients who received exa-cel therapy is considered missing information and further characterisation is needed.

Exa-cel must not be administered during pregnancy because of the risk associated with myeloablative conditioning. Breastfeeding should be discontinued during conditioning due to the potential risks associated with myeloablative conditioning. The decision to breastfeed after exa-cel treatment should be discussed with the HCP, taking into account the benefit of breastfeeding for the child versus any potential adverse effect from exa-cel or from the underlying maternal condition.

Population in need of further characterisation
The outcomes of pregnancy and lactation in patients who receive exa-cel therapy will be evaluated as missing information in post-authorisation surveillance.

SVII.3.2.3 Missing Information – Use in patients >35 years of age

Evidence source
Patients >35 years of age were not included in pivotal Phase 1/2/3 clinical studies in subjects with TDT (Study 111) or SCD (Study 121). Patients >35 years of age are eligible for exa-cel

therapy in the post-authorisation setting if the benefit is considered to outweigh the risks; therefore, use in this age group is considered missing information and further characterisation is needed.

Population in need of further characterisation
Use of exa-cel therapy in patients >35 years of age will be evaluated through post-authorisation surveillance.

SVIII Summary of Safety Concerns

Table 17 Summary of Safety Concerns

Important identified risks	• Delayed platelet engraftment
Important potential risks	• Neutrophil engraftment failure • Gene editing-related oncogenesis
Missing information	• Long-term effects • Pregnancy and lactation • Use in patients >35 years of age

PART III Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for: pregnancy and lactation, time to platelet engraftment, neutrophil engraftment failure, and haematologic malignancy.

The purpose of these questionnaires is to obtain structured information on each topic in the post-authorisation setting. A copy of each questionnaire is provided in Annex 4 Specific adverse event follow-up form.

III.2 Additional Pharmacovigilance Activities

III.2.1 Study 101 Post-authorisation safety study (PASS)

Study 101 is a long-term, registry-based study evaluating the long-term safety and effectiveness outcomes in patients who received Casgevy for treatment of TDT or SCD.

Rationale and study objectives

- To evaluate the long-term safety and effectiveness outcomes in patients who received Casgevy for treatment of TDT or SCD in comparison to patients receiving allogeneic HSCT
- Safety concerns evaluated:
  - Delayed platelet engraftment
  - Neutrophil engraftment failure
  - Gene editing-related oncogenesis
  - Long-term effects

- Pregnancy outcomes
- Use in patients >35 years of age

Study design: Post-authorisation, long-term, prospective observational cohort study using primary and secondary data collected by established registries (Center for International Blood and Marrow Transplant Research [CIBMTR] and European Group for Blood and Marrow Transplantation [EBMT]). Both aggregate and patient-level data will be requested from the registries, pending patient consent. Enrolled patients will be followed for up to 15 years.

Study population: Patients with TDT or SCD treated with Casgevy (exa-cel cohorts) or allogeneic HSCT (comparator cohorts) in participating centres reporting data to the CIBMTR and EBMT registries. Participating centres for patient enrolment will initially include centres located in France, Germany, Italy, and the UK, as well as the US; additional centres and / or nations may be included with expanded exa-cel availability.

Milestones:

Table 18 Study 101 (PASS) Milestones

Milestone	Data Included	Planned Date[a]
Start of data collection	-	2024
End of data collection	-	2042
Protocol submission	-	31 March 2024
Registration in the EU PAS register	-	Following protocol approval
Progress Report 4	Tentatively through 12/31/2027	31 December 2028[b]
Progress Report 5	Tentatively through 12/31/2028	31 December 2029
Interim Report 2	Tentatively through 12/31/2032 (all enrolled patients anticipated to reach 5 years of follow-up)	31 December 2033[b]
Interim Report 3	Tentatively through 12/31/2037 (all enrolled patients anticipated to reach 10 years of follow-up)	31 December 2038
Final Report	Tentatively through 12/31/2042 (all enrolled patients anticipated to reach 15 years of follow-up)	31 December 2043
Publication	To be determined	To be determined

EU: European Union; MA: market authorisation; PAS: post-authorisation study; PASS: post-authorisation safety study

Note: Progress and interim reports will be summarised and included within the Periodic Safety Update Report.

[a] Per EU GVP Module VIII.B.2, the start and end of data collection for secondary use of data are when the analytical datasets are available.

[b] Interim Analysis 1 and Progress Reports 1, 2, and 3 will be provided as special obligations in the context of a conditional MA. Hence the PASS milestones begin with Interim Report 2 and Progress Report 4.

III.2.2 Healthcare Professional (HCP) Survey (PASS)

Healthcare professional (HCP) Survey to assess the effectiveness of the additional risk minimisation measures (aRMMs) for exagamglogene autotemcel (Casgevy)

Rationale and study objectives: The aRMM for Casgevy include a Guide for HCPs, a Patient Card, and a Guide for Patients/Carers which address the important identified risk of delayed platelet engraftment, the important potential risks of neutrophil engraftment failure

and gene editing-related oncogenesis, and missing information on long-term effects. These materials will be distributed to HCPs at centres with experience in HSCT who are authorised to treat patients with Casgevy. HCPs will be required to provide the Patient Card and Guide for Patients/Carers to patients/carers before Casgevy treatment decision. The HCP Survey will assess the following:

1. The HCPs' understanding of the important safety information detailed in the Guide for HCPs regarding the important identified risk of delayed platelet engraftment, the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis, and the missing information on long-term effects.
2. The HCPs' awareness of aRMM tools.
3. The HCPs' utilisation of aRMM tools (behaviour).

Study design: This is a multi-national, observational cross-sectional study. A survey will be administered to HCPs at centres that are authorised to treat patients with Casgevy.

Study population: The survey will be administered to HCPs at centres that are authorised to treat patients with Casgevy in at least 3 European countries (Germany, Italy, and France anticipated), but the final number and list of countries will depend on the commercial availability of Casgevy in the EU (e.g., Spain, Austria, and Denmark may also be included). Screening questions will be used to determine respondent eligibility for the survey.

Milestones:

Table 19 HCP Survey (PASS) Milestones

Milestone	Planned Date
Start of data collection	18 months after first market launch in the EU
End of data collection	24 months after first market launch in the EU
Protocol submission	Within 6 months after MA
Registration in the EU PAS register	Following protocol approval
Final Report	30 months after first market launch in the EU

EU: European Union; HCP: healthcare provider; MA: market authorisation; PAS: post-authorisation study; PASS: post-authorisation safety study

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 20 Planned and Ongoing Post-authorisation Studies in the Pharmacovigilance Plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
Study 101 (PASS) Planned	**Primary Objective** • Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD • Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT	• Delayed platelet engraftment • Neutrophil engraftment failure • Gene editing-related oncogenesis	Progress Reports	31 December 2028/2029
			Interim Reports	31 December 2033/2038
			Final Report	31 December 2043

Table 20 Planned and Ongoing Post-authorisation Studies in the Pharmacovigilance Plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	Secondary Objectives • Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD • Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT	• Long-term effects • Pregnancy • Use in patients >35 years of age		
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
Not applicable				
Category 3 – Required additional PV activities (by the competent authority)				
HCP Survey (PASS) Planned	**Study Objective** • Assess the HCPs' understanding of the important safety information detailed in the Guide for HCPs • Assess the HCPs' awareness of the aRMM tools • Assess the HCPs' utilisation of aRMM tools (behaviour)	• Delayed platelet engraftment • Neutrophil engraftment failure • Gene editing-related oncogenesis • Long-term effects	Final Report	30 months after first market launch in the EU

allo: allogeneic; exa-cel: exagamglogene autotemcel; CRISPR-Cas9: clustered regularly interspaced short palindromic repeats-associated 9 nuclease; HbF: foetal haemoglobin; HCP: healthcare professional; hHSPCs: human haematopoietic stem and progenitor cells; HSCT: haematopoietic stem cell transplant; MA: marketing authorisation; PASS: post-authorisation safety study; PSUR: periodic safety update report; PV: pharmacovigilance; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

Note: Study 101 (PASS) progress and interim reports will also be summarised and included within the PSUR.

PART IV Plans for Post-authorisation Efficacy Studies

IV.1 Conditions of the Marketing Authorisation

Not applicable

IV.2 Specific Obligations

IV.2.1 Study 101 Post-authorisation safety study (PASS)

Study 101 is a long-term, registry-based study evaluating the long-term safety and effectiveness outcomes in patients who received Casgevy for treatment of TDT or SCD.

See Part III.2.1 for a full description of this study.

Rationale and study objectives

- Efficacy concerns evaluated:
  - Efficacy in additional subjects

Milestones: Progress Reports 1, 2, and 3: 31 August 2024/2025/2026; Interim Report 1: 31 December 2027 (reports will also be summarised in the periodic safety update reports [PSURs])

IV.2.2 Study 111 in subjects with TDT ages 12 to 35 years

Study 111 is an ongoing interventional study evaluating the safety and efficacy of exa-cel in subjects 12 to 35 years of age with TDT.

Rationale and Study Objectives:

- To evaluate the safety and efficacy of exa-cel in subjects with TDT
- Efficacy concerns evaluated:
  - Efficacy in additional subjects
- Safety concerns evaluated:
  - Delayed platelet engraftment
  - Neutrophil engraftment failure

Study Design: Phase 1/2/3, open-label, single-arm, single-dose, multi-site study

Study Population: Subjects 12 to 35 years of age with TDT

Milestones: Final Report: 31 August 2026

IV.2.3 Study 121 in subjects with SCD ages 12 to 35 years

Study 121 is an ongoing interventional study evaluating the safety and efficacy of exa-cel in subjects 12 to 35 years of age with SCD.

Rationale and Study Objectives:

- To evaluate the safety and efficacy of exa-cel in subjects with SCD
- Efficacy concerns evaluated:
  - Efficacy in additional subjects
- Safety concerns evaluated:
  - Delayed platelet engraftment
  - Neutrophil engraftment failure

Study Design: Phase 1/2/3, open-label, single-arm, single-dose, multi-site study

Study Population: Subjects 12 to 35 years of age with SCD

Milestones: Final Report: 31 August 2026

IV.2.4 Study 131 Long-term follow-up study in subjects with TDT and SCD

Study 131 is an ongoing follow-up clinical study evaluating the long-term safety and efficacy of exa-cel for 15 years after exa-cel infusion in subjects with TDT and SCD who received exa-cel in a previous study.

Rationale and Study Objectives:

- To evaluate the long-term safety and efficacy of exa-cel treatment

- Efficacy concerns evaluated:
  - Efficacy in additional subjects
- Safety concerns evaluated:
  - Gene editing-related oncogenesis
  - Long-term effects
  - Pregnancy and lactation

Study Design: Long-term follow-up, multi-site, rollover study

Study Population: Subjects with TDT and SCD who received exa-cel treatment

Milestones: Interim Reports: 31 August 2026/2029 (reports will also be summarised in the PSURs)

- The 2026 report will include all subjects dosed in Study 111 (TDT; N=56) and Study 121 (SCD; N=45) completing 2 years of follow-up after exa-cel infusion.
- The 2029 report will include all subjects dosed in Study 111 (TDT; N=56) and Study 121 (SCD; N=45) completing 5 years of follow-up after exa-cel infusion; the total anticipated number of subjects included is 136 subjects with at least 2 years of follow-up and 108 subjects with at least 5 years of follow-up.

IV.2.5 Study 151 in subjects with SCD ages 2 to 11 years

Study 151 is an ongoing interventional study evaluating the safety and efficacy of exa-cel in subjects 2 to 11 years of age with SCD.

Rationale and Study Objectives:

- To evaluate the efficacy, safety, and tolerability of exa-cel in paediatric subjects with severe SCD
- Efficacy concerns evaluated:
  - Efficacy in additional subjects
- Safety concerns evaluated:
  - Delayed platelet engraftment
  - Neutrophil engraftment failure

Study Design: Phase 3, open-label, single-arm, single-dose, multi-site study

Study Population: Subjects 2 to 11 years of age with SCD

Milestones: Final Report: 31 December 2027

IV.2.6 Study 161 in subjects with TDT or SCD ages 12 to 35 years

Study 161 is an ongoing interventional study evaluating the efficacy and safety of exa-cel in subjects 12 to 35 years of age with SCD.

Rationale and Study Objectives:

- To evaluate the foetal haemoglobin (HbF) levels over time after a single dose, efficacy, and safety of exa-cel in subjects with TDT or severe SCD
- Efficacy concerns evaluated:

- Efficacy in additional subjects

- Safety concerns evaluated:
  - Delayed platelet engraftment
  - Neutrophil engraftment failure

Study Design: Phase 3b, open-label, single-arm, single-dose, multi-site study

Study Population: Subjects 12 to 35 years of age with TDT or SCD

Milestones: Interim Report: 31 December 2027 (anticipated to include 7 subjects with TDT and 12 subjects with SCD with 1-year of follow-up after exa-cel infusion)

IV.2.7 Study 171 in subjects with SCD ages 12 to 35 years

Study 171 is a planned interventional study evaluating the efficacy and safety of exa-cel in subjects 12 to 35 years of age with severe SCD, βS/βC genotype (HbSC).

Rationale and Study Objectives:

- To evaluate the efficacy and safety of exa-cel in subjects with SCD, HbSC genotype
- Efficacy concerns evaluated:
  - Efficacy in additional subjects
- Safety concerns evaluated:
  - Delayed platelet engraftment
  - Neutrophil engraftment failure

Study Design: Phase 3, open-label, single-arm, single-dose, multi-site study

Study Population: Subjects 12 to 35 years of age with SCD

Milestones: Final Report: 30 June 2032

IV.3 Summary Table of Post-authorisation Efficacy Studies

Table 21 Planned and Ongoing Post-authorisation Efficacy Studies

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study 101 (PASS) Planned	**Primary Objective** • Evaluate long-term safety outcomes in patients who received exa-cel for treatment of TDT or SCD	• Efficacy in additional subjects	Progress Reports	31 August 2024/2025/ 2026

Table 21 Planned and Ongoing Post-authorisation Efficacy Studies

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
	• 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 Objectives** • Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD • Evaluate long-term effectiveness outcomes in patients who received exa-cel for treatment of TDT or SCD in comparison to patients receiving allo-HSCT		Interim Report 1	31 December 2027
Study 111 in subjects with TDT ages 12 to 35 years Ongoing	**Primary Objective** • To evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified CD34^{+} hHSPCs (exa-cel) **Secondary Objectives** • To quantify percentage of edited alleles in peripheral blood leukocytes and CD34^{+} cells of the bone marrow • To assess the production of HbF after exa-cel infusion • To assess the effects of infusion of exa-cel on disease-specific events and clinical status **Exploratory Objective** • To assess the ability of biomarkers to characterise exa-cel effect and predict treatment outcomes	• Efficacy in additional subjects	Final Report	31 August 2026
Study 121 in subjects with SCD ages 12 to 35 years Ongoing	**Primary Objective** • To evaluate the safety and efficacy of a single dose of autologous CRISPR-Cas9 modified CD34^{+} hHSPCs (exa-cel) **Secondary Objectives** • Assess the effects of infusion of exa-cel on disease-specific events and clinical status • Quantify gene editing efficiency **Exploratory Objective** • Assess the ability of biomarkers to characterise exa-cel effect and predict treatment outcomes	• Efficacy in additional subjects	Final Report	31 August 2026
Study 131 Long-term follow-up study in subjects with TDT and SCD Ongoing	In subjects who received exa-cel for treatment of TDT or SCD **Primary Objective** • To evaluate long-term safety for 15 years after exa-cel infusion **Secondary Objective** • To evaluate efficacy of exa-cel for 15 years after exa-cel infusion	• Efficacy in additional subjects	Interim Reports	31 August 2026/2029

Table 21 Planned and Ongoing Post-authorisation Efficacy Studies

Study/Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Study 151 in subjects with SCD ages 2 to 11 years Ongoing	**Primary Objective** • To evaluate efficacy of a single dose of exa-cel in paediatric subjects with severe SCD **Secondary Objective** • To evaluate safety and tolerability of a single dose of exa-cel • Assess the effects of infusion of exa-cel on disease-specific events and clinical status Quantify gene editing efficiency	• Efficacy in additional subjects	Final Report	31 December 2027
Study 161 in subjects with TDT or SCD ages 12 to 35 years Ongoing	**Primary Objective** • To assess HbF levels over time, after a single dose of exa-cel in adolescent and adult subjects with either TDT or severe SCD **Secondary Objective** • To evaluate efficacy and safety of a single dose of exa-cel • Assess the effects of infusion of exa-cel on disease-specific events and clinical status • Quantify gene editing efficiency	• Efficacy in additional subjects	Interim Report	31 December 2027
Study 171 in subjects with SCD ages 12 to 35 years Planned	**Primary Objective** • To evaluate efficacy of a single dose of exa-cel in adolescent and adult subjects with severe SCD, HbSC genotype **Secondary Objectives** • To evaluate safety of a single dose of exa-cel in adolescent and adult subjects with SCD, HbSC genotype • Assess the effects of infusion of exa-cel on disease-specific events and clinical status • Quantify gene editing efficiency	• Efficacy in additional subjects	Final Report	30 June 2032

allo: allogeneic; exa-cel: exagamglogene autotemcel; HbF: foetal haemoglobin; HbSC: βS/βC; HSCT: haematopoietic stem cell transplant; PASS: post-authorisation safety study; PSUR: periodic safety update report; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

Note: Study 101 (PASS) progress and interim reports and Study 131 interim reports will also be summarised and included within the Periodic Safety Update Report.

PART V Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

V.1 Routine Risk Minimisation Measures

Table 22 Routine Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Activities
Delayed platelet engraftment	**Routine risk communication:** SmPC Sections 4.1, 4.2, and 4.4 PL Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measure to address the risk: • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of exa-cel must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Recommendations for monitoring platelet counts and managing symptoms of bleeding are provided in SmPC Section 4.4. • Advice on how to identify symptoms of bleeding and when to contact the doctor is given in PL Sections 2 and 4.
	Other routine risk minimisation measures beyond the Product Information: Restricted prescription medicine
Neutrophil engraftment failure	**Routine risk communication:** SmPC Sections 4.1, 4.2, and 4.4 PL Sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measure to address the risk: • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of exa-cel must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Collection of unmodified rescue $CD34^+$ cells is required prior to myeloablative conditioning and infusion with exa-cel, as outlined in SmPC Section 4.2. • Guidance for administering unmodified rescue cells in the event of neutrophil engraftment failure is provided in SmPC Sections 4.2 and 4.4. • Recommendations for monitoring neutrophil counts and managing infections are provided in SmPC Section 4.4. • Information on what to expect if engraftment fails is provided in PL Section 2. • Advice on how to identify symptoms of infection and when to contact the doctor is given in PL Sections 2 and 4.
	Other routine risk minimisation measures beyond the Product Information: Restricted prescription medicine
Gene editing-related oncogenesis	**Routine risk communication:** SmPC Section 4.4
	Routine risk minimisation activities recommending specific clinical measure to address the risk: • Description that there have been no cases of myelodysplasia, leukaemia, or lymphoma from the clinical studies • As a theoretical risk, recommend monitoring at least annually (including complete blood count) for 15 years after treatment.
	Other routine risk minimisation measures beyond the Product Information:

Table 22 Routine Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Activities
	Restricted prescription medicine
Long-term effects	**Routine risk communication:** SmPC Section 4.4 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: • Recommendation for long-term follow up is provided in SmPC Section 4.4. • Expectations for long-term monitoring are described in PL Section 2.
	Other routine risk minimisation measures beyond the Product Information: Restricted prescription medicine
Pregnancy and lactation	**Routine risk communication:** SmPC Section 4.6 PL Section 2
	Routine risk minimisation activities recommending specific clinical measure to address the risk: • Recommendations for contraception use, breastfeeding, and pregnancy, including a negative pregnancy test prior to the start of any treatment, are provided in SmPC Section 4.6. • Exa-cel must not be administered during pregnancy due to risks associated with myeloablative conditioning, as stated in SmPC Section 4.6. • Breastfeeding should be discontinued during myeloablative conditioning due to the associated risks as stated in SmPC Section 4.6. • Recommendations to discuss pregnancy and breastfeeding after exa-cel are provided for patients in SmPC Section 4.6. • Expectations for use of contraception, pregnancy testing, and breastfeeding are described in PL Section 2. • Advice for talking to the doctor prior to starting treatment is given in PL Section 2.
	Other routine risk minimisation measures beyond the Product Information: Restricted prescription medicine
Use in patients >35 years of age	**Routine risk communication:** SmPC Section 4.2 Restricted prescription medicine
	Routine risk minimisation activities recommending specific clinical measure to address the risk: As Casgevy has not been studied in patients >35 years of age, recommendation to consider the benefits of treatment against the risks of HSCT provided in SmPC Section 4.2.
	Other routine risk minimisation measures beyond the Product Information: Restricted prescription medicine

HSCT: haematopoietic stem cell transplantation; PL: Package Leaflet; SCD: sickle cell disease; SmPC: Summary of Product Characteristics; TDT: transfusion-dependent β-thalassemia

V.2 Additional Risk Minimisation Measures

The additional risk minimisation measures will address the following risks:

- Delayed platelet engraftment (important identified risk)
- Neutrophil engraftment failure (important potential risk)
- Gene editing-related oncogenesis (important potential risk)
- Long-term effects (missing information)

Table 23 Additional Risk Minimisation Measure Tools

	Safety Concern Addressed by Tool			
Additional Risk Minimisation Tool	**Delayed Platelet Engraftment**	**Neutrophil Engraftment Failure**	**Gene Editing-Related Oncogenesis**	**Long-term Effects**
Guide to Healthcare Professionals	Yes	Yes	Yes	Yes
Guide for Patients/Carers	Yes	Yes	Yes	Yes
Patient Card	Yes	Yes	Yes	No

V.2.1 Guide for Healthcare Professionals

Objectives
To advise HCPs regarding the important identified risk of delayed platelet engraftment, the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis, and the missing information of long-term effects of Casgevy, the need to monitor patients regarding these safety concerns, and to counsel patients regarding the risks and missing information.

Rationale for the additional risk minimisation activity
In clinical Studies 111 and 121, median times to platelet engraftment after exa-cel infusion were 44.0 days (range 20 to 200 days) for subjects with TDT and 35.0 days (range 23 to 126 days) for subjects with SCD. Although there was no association observed between bleeding events and time to platelet engraftment, generally the patient is at increased risk of bleeding prior to platelet engraftment.

Whilst there were no cases of neutrophil engraftment failure or gene editing-related oncogenesis in these 2 studies, it is important for HCPs to be aware that neutrophil engraftment failure can be an outcome of any HSCT procedure and gene editing-related oncogenesis is theoretically possible.

Additionally, there is limited information regarding the long-term effects of exa-cel. Therefore, HCPs should encourage patients to participate in the long-term, registry-based study (Study 101).

Target audience and planned distribution path
The target audience will be HCPs with experience in HSCT and in the treatment of patients with β-haemoglobinopathies who will treat patients with exa-cel.

Exa-cel must be administered in an authorised treatment centre by a physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies. Agreements for stem cell collection, quality and product supply will be in place between the MAH and

each treatment centre prior to the supply of exa-cel. Product specific training, including the Guide for HCPs, will be completed by all HCPs involved in treating patients with exa-cel within authorised treatment centres.

The MAH will have trained field and headquarter staff in place to respond to questions raised by treatment centres and provide additional supplies of the Guide for HCPs as necessary.

Plans to evaluate the effectiveness of the interventions and criteria for success
An HCP Survey (PASS) will be conducted to assess HCPs understanding of the key risk messages, as well as awareness and utilisation (behaviour) of the aRMM tools. The education program will be considered effective if at least 75% of respondents understand the key messages, and at least 75% are aware of aRMM tools and utilised them in clinical practice. The results will be presented in the Casgevy Periodic Safety Update Reports.

V.2.2 Patient Card

Objectives
To ensure that information regarding the patient's treatment with exa-cel and the important identified risk of delayed platelet engraftment and the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis is held by the patient and can be made available to relevant HCPs who may treat the patient after exa-cel treatment. This would include any HCPs treating the patient for conditions other than that being treated by exa-cel and any HCPs treating the patient in an emergency.

Rationale for the additional risk minimisation activity
In clinical Studies 111 and 121, median times to platelet engraftment after exa-cel infusion were 44.0 days (range 20 to 200 days) for subjects with TDT and 35.0 days (range 23 to 126 days) for subjects with SCD. Although there was no association observed between bleeding events and time to platelet engraftment, generally the patient is at increased risk of bleeding prior to platelet engraftment.

It is important that patients and all HCPs who may treat the patient after exa-cel treatment, in the period prior to platelet levels returning to a safe level, are aware of this risk.

Whilst there were no cases of neutrophil engraftment failure or gene editing-related oncogenesis in Studies 111 and 121, it is important for patients and all HCPs who may treat the patient after exa-cel treatment to be aware that neutrophil engraftment failure can be an outcome of any HSCT procedure and gene editing-related oncogenesis is theoretically possible.

Target audience and planned distribution path
The target audience for the Patient Card will be patients with TDT or SCD who are considering treatment with exa-cel. HCPs who treat a patient with exa-cel will be required to provide the Patient Card to the patient prior to the patient's decision for exa-cel treatment. The tools are part of the training that an HCP will undergo prior to administering exa-cel (see below). In the event that the patient loses the Patient Card, the HCP will be able to provide a replacement.

Exa-cel must be administered in an authorised treatment centre by a physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies. Agreements for stem cell collection, quality and product supply will be in place between the MAH and each treatment centre prior to the supply of exa-cel. Product specific training, including the Patient Cards, will be completed by all HCPs involved in treating patients with exa-cel within authorised treatment centres.

The MAH will have trained field and headquarter staff in place to respond to questions raised by treatment centres and provide additional supplies of the Patient Cards as necessary.

Plans to evaluate the effectiveness of the interventions and criteria for success
MAH will have a process recording that HCPs completed their obligations to provide and explain the Patient Card prior to the patient's decision for exa-cel treatment. In addition, the HCP Survey (PASS) will assess the HCPs' awareness and utilisation of the Patient Card, with the program considered successful if at least 75% of the responders are aware of the Patient Card and utilise it in clinical practice.

V.2.3 Guide for Patients/Carers

Objectives
To advise patients/carers regarding the important identified risk of delayed platelet engraftment and the important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis; to alert patients to seek medical assistance if they experience any symptoms of bleeding; to inform the patient of the potential for neutrophil engraftment failure; to inform patients of the potential for gene editing-related oncogenesis; to inform patients of the limited information regarding the long-term effects of exa-cel.

Rationale for the additional risk minimisation activity
In clinical Studies 111 and 121, median times to platelet engraftment after exa-cel infusion were 44.0 days (range 20 to 200 days) for subjects with TDT and 35.0 days (range 23 to 126 days) for subjects with SCD. Although there was no association observed between bleeding events and time to platelet engraftment, generally the patient is at increased risk of bleeding prior to platelet engraftment and should be monitored closely for bleeding.

Whilst there were no cases of neutrophil engraftment failure or gene editing-related oncogenesis in these two studies, it is important for patients/carers to be aware of these potential risks as neutrophil engraftment failure can be an outcome of any HSCT procedure and gene editing-related oncogenesis is theoretically possible. Further, if neutrophil engraftment failure occurs, the patient will have received no benefit from treatment.

Additionally, there is limited information regarding the long-term effects of exa-cel. Therefore, patients should be encouraged to participate in the long-term, registry-based study (Study 101).

Target audience and planned distribution path
The target audience for the Guide for Patients/Carers will be patients with TDT or SCD who are considering treatment with exa-cel or carers, as appropriate. HCPs who treat a patient with exa-cel will be required to provide the Guide for Patients/Carers to the patient prior to the decision for exa-cel treatment. The tools are part of the training that an HCP will undergo prior to administering exa-cel (see below). In the event that the patient loses the Guide for Patients/Carers, the HCP will be able to provide a replacement.

Exa-cel must be administered in an authorised treatment centre by a physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies. Agreements for stem cell collection, quality and product supply will be in place between the MAH and each treatment centre prior to the supply of exa-cel. Product specific training, including the Guide for Patients/Carers, will be completed by all HCPs involved in treating patients with exa-cel within authorised treatment centres.

The MAH will have trained field and headquarter staff in place to respond to questions raised by treatment centres and provide additional supplies of the Guide for Patients/Carers as necessary.

Plans to evaluate the effectiveness of the interventions and criteria for success
MAH will have a process recording that HCPs completed their obligations to provide and explain the Guide for Patients/Carers prior to the patient's decision for exa-cel treatment. In addition, the HCP Survey (PASS) will assess the HCPs' awareness and utilisation of the Patient Card, with the program considered successful if at least 75% of the responders are aware of and utilise it in clinical practice.

V.3 Summary of Risk Minimisation Measures

Table 24 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Delayed platelet engraftment	**Routine risk minimisation measures:** SmPC Sections 4.1, 4.2, and 4.4 • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of exa-cel must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Recommendations for monitoring platelet counts and managing symptoms of bleeding are provided in SmPC Section 4.4. PL Sections 2 and 4 • Advice on how to identify symptoms of bleeding and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine **Additional risk minimisation measures:** • Guide for HCPs • Patient Card • Guide for Patients/Carers	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Platelet Engraftment Safety Information Collection Questionnaire **Additional PV activities:** • Study 101 (PASS) Progress reports: 31 December 2028/2029; Interim reports: 31 December 2033/2038; Final report: 31 December 2043 • HCP Survey (PASS) Final Report: 30 months after first market launch in the EU *Efficacy studies that will provide relevant safety results:* • Study 101 (PASS) Progress reports: 31 August 2024/2025/2026 Interim report: 31 December 2027 • Study 111 in subjects with TDT ages 12 to 35 years; Final Report: 31 August 2026 • Study 121 in subjects with SCD ages 12 to 35 years; Final Report: 31 August 2026 • Study 151 in subjects with SCD ages 2 to 11 years; Final Report: 31 December 2027 • Study 161 in subjects with TDT or SCD ages 12 to 35 years; Interim Report: 31 December 2027 • Study 171 in subjects with SCD ages 12 to 35 years; Final Report: 30 June 2032
Neutrophil engraftment failure	**Routine risk minimisation measures:** SmPC Sections 4.1, 4.2, and 4.4 • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of exa-cel must be performed in a treatment centre by physician(s) with	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Neutrophil Engraftment Failure Safety Information Collection Questionnaire

Table 24 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Collection of unmodified rescue CD34+ stem cells is required prior to myeloablative conditioning and infusion with exa-cel, as outlined in SmPC Section 4.2. • Guidance for administering unmodified rescue cells in the event of neutrophil engraftment failure is provided in SmPC Sections 4.2 and 4.4. • Recommendations for monitoring neutrophil counts and managing infections are provided in SmPC Section 4.4. PL Sections 2 and 4 • Information on what to expect if engraftment fails is provided in PL Section 2. • Advice on how to identify symptoms of infection and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine **Additional risk minimisation measures:** • Guide for HCPs • Patient Card • Guide for Patients/Carers	**Additional PV activities:** • Study 101(PASS) Progress reports: 31 December 2028/2029; Interim reports: 31 December 2033/2038; Final report: 31 December 2043 • HCP Survey (PASS) Final Report: 30 months after first market launch in the EU *Efficacy studies that will provide relevant safety results:* • Study 101 (PASS) Progress reports: 31 August 2024/2025/2026; Interim report: 31 December 2027 • Study 111 in subjects with TDT ages 12 to 35 years; Final Report: 31 August 2026 • Study 121 in subjects with SCD ages 12 to 35 years; Final Report: 31 August 2026 • Study 151 in subjects with SCD ages 2 to 11 years; Final Report: 31 December 2027 • Study 161 in subjects with TDT or SCD ages 12 to 35 years; Interim Report: 31 December 2027 • Study 171 in subjects with SCD ages 12 to 35 years; Final Report: 30 June 2032
Gene editing-related oncogenesis	**Routine risk minimisation measures:** SmPC Section 4.4 • Description of the lack of myelodysplasia, leukaemia, or lymphoma from the clinical studies and a recommendation to monitor at least annually (including complete blood count) for 15 years after treatment is provided in SmPC Section 4.4 Restricted prescription medicine **Additional risk minimisation measures:** • Guide for HCPs • Patient Card • Guide for Patients/Carers	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Haematologic Malignancy Safety Information Collection Questionnaire **Additional PV activities:** • Study 101 (PASS) Progress reports: 31 December 2028/2029; Interim reports: 31 December 2033/2038; Final report: 31 December 2043 • HCP Survey (PASS) Final Report: 30 months after first market launch in the EU *Efficacy studies that will provide relevant safety results:* • Study 101 (PASS) Progress reports: 31 August

Table 24 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		2024/2025/2026; Interim report: 31 December 2027 • Study 131 Long-term follow-up study in subjects with TDT or SCD; Interim Reports: 31 August 2026/2029
Long-term effects	**Routine risk minimisation measures:** SmPC Section 4.4 • Recommendation for long-term follow up is provided in SmPC Section 4.4. PL Section 2 • Expectations for long-term monitoring are described in PL Section 2. Restricted prescription medicine **Additional risk minimisation measures:** • Guide for HCPs • Guide for Patients/Carers	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Study 101 (PASS) Progress reports: 31 December 2028/2029; Interim reports: 31 December 2033/2038; Final report: 31 December 2043 • HCP Survey (PASS) FinalReport: 30 months after first market launch in the EU *Efficacy studies that will provide relevant safety results:* • Study 101 (PASS) Progress reports: 31 August 2024/2025/2026; Interim report: 31 December 2027 • Study 131 Long-term follow-up study in subjects with TDT or SCD; Interim Reports: 31 August 2026/2029
Pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6 • Recommendations for contraception use, breastfeeding, and pregnancy, including a negative pregnancy test prior to the start of any treatment, are provided in SmPC Section 4.6. • Exa-cel must not be administered during pregnancy or breastfeeding due to risks associated with myeloablative conditioning, as stated in SmPC Section 4.6 PL Section 2 • Expectations for use of contraception, pregnancy testing, and breastfeeding are described in PL Section 2. • Advice for talking to the doctor prior to starting treatment is given in PL Section 2. Restricted prescription medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy and Lactation Safety Information Collection Questionnaire **Additional PV activities:** • Study 101 (PASS) Progress reports: 31 December 2028/2029; Interim reports: 31 December 2033/2038; Final report: 31 December 2043 *Efficacy studies that will provide relevant safety results:* • Study 101 (PASS) Progress reports: 31 August 2024/2025/2026; Interim report: 31 December 2027 • Study 131 Long-term follow-up study in subjects with TDT or SCD;

Table 24 Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Interim Reports: 31 August 2026/2029
Use in patients >35 years of age	**Routine risk minimisation measures:** SmPC Section 4.2 • Recommendation to consider the benefits of treatment against the risks of HSCT Restricted prescription medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Study 101 (PASS) Progress reports: 31 December 2028/2029; Interim reports: 31 December 2033/2038; Final report: 31 December 2043 *Efficacy studies that will provide relevant safety results:* • Study 101 (PASS) Progress reports: 31 August 2024/2025/2026; Interim report: 31 December 2027

EU: European Union; HSCT: haematopoietic stem cell transplantation; PASS: Post-authorisation safety study; PL: Package Leaflet; PV: pharmacovigilance; Q4: Quarter 4; SCD: sickle cell disease; SmPC: Summary of Product Characteristics; TDT: transfusion-dependent β-thalassemia

Note: Study 101 (PASS) progress and interim reports and Study 131 interim reports will also be summarised and included within the Periodic Safety Update Report.

PART VI Summary of the RMP

Summary of Risk Management Plan for Casgevy (exagamglogene autotemcel)

This is a summary of the risk management plan (RMP) for CASGEVY. The RMP details important risks of CASGEVY, how these risks can be minimised, and how more information will be obtained about CASGEVY's risks and uncertainties (missing information).

CASGEVY's SmPC and its package leaflet (PL) give essential information to healthcare professionals and patients on how CASGEVY should be used.

This summary of the RMP for CASGEVY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current ones will be included in updates of CASGEVY's RMP.

I. The medicine and what it is used for

CASGEVY is authorised for the treatment of transfusion dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available (see SmPC for the full indication). CASGEVY is also authorised for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom HSC transplantation is appropriate and an HLA-matched related HSC donor is not available (see SmPC for the full indication).

CASGEVY is a one-time gene therapy. It is made specifically for each patient, using the patient's own blood stem cells. Blood stem cells are cells that can turn into other blood cells including red cells, white cells, and platelets. The cells are taken from the patient, then are genetically modified and they are given back to the same patient as a stem cell transplant. Further information about the evaluation of CASGEVY's benefits can be found in CASGEVY's EPAR, including its plain-language summary, available on the EMA website under the medicine's webpage: link to the EPAR summary landing page.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of CASGEVY, together with measures to minimise such risks and the proposed studies for learning more about CASGEVY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

If important information that may affect the safe use of CASGEVY, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of CASGEVY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CASGEVY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term follow up of the medicine).

List of important risks and missing information	
Important identified risks	• Delayed platelet engraftment
Important potential risks	• Neutrophil engraftment failure • Gene editing-related oncogenesis
Missing information	• Long-term effects • Pregnancy and lactation • Use in patients >35 years of age

II.B Summary of important risks

Delayed platelet engraftment (Important identified risk)	
Evidence for linking the risk to the medicine	In the pivotal Phase 1/2/3 clinical study in subjects 12 to 35 years of age with TDT (Study 111) and SCD (Study 121), median time to platelet engraftment after CASGEVY infusion was comparatively longer than reported in allogeneic HSCT; however, it was consistent with the median time reported in other genetic therapies involving HSCT. There was no association observed between bleeding AEs and time to platelet engraftment after CASGEVY infusion. However, thrombocytopenia following myeloablative conditioning is a risk factor for serious bleeding-related complications, with the highest risk occurring prior to platelet engraftment. As such, delayed platelet engraftment is considered and important identified risk.
Risk factors and risk groups	Following infusion with CASGEVY, subjects with TDT without a spleen (i.e., splenectomised) had an earlier median time to platelet engraftment than subjects with an intact spleen. This finding is similar to data from allogenic HSCT and other genetic therapies for β-thalassemia major.
Risk minimisation measures	<u>Routine Risk Minimisation Measures</u> SmPC Sections 4.1, 4.2, and 4.4: • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of CASGEVY must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Recommendations for monitoring platelet counts and managing symptoms of bleeding are provided in SmPC Section 4.4. PL Sections 2 and 4: • Advice to on how to identify symptoms of bleeding and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine <u>Additional Risk Minimisation Measures</u> • Guide for HCPs • Patient Card • Guide for Patients/Carers

Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD ages 12 to 35 years • Study 151 in subjects with SCD ages 2 to 11 years • Study 161 in subjects with TDT or SCD ages 12 to 35 years • Study 171 in subjects with SCD ages 12 to 35 years See Section II.C of this summary for an overview of the post-authorisation development plan.
Neutrophil engraftment failure (Important potential risk)	
Evidence for linking the risk to the medicine	Neutrophil engraftment failure is considered an important potential risk because of the possibility for neutrophil engraftment failure to be an outcome of any myeloablation and bone marrow transplantation. Failure to achieve neutrophil engraftment would require a subsequent HSCT procedure with unmodified rescue $CD34^+$ stem cells, thereby negating beneficial effects of CASGEVY gene therapy. However, in the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) and SCD (Study 121), there was no evidence of neutrophil engraftment failure after CASGEVY infusion and this risk is considered potential.
Risk factors and risk groups	As no subjects with TDT or SCD failed to achieve neutrophil engraftment following CASGEVY infusion, no risk factors or risk groups were identified in the clinical programme.
Risk minimisation measures	<u>Routine Risk Minimisation Measures</u> SmPC Sections 4.1, 4.2, and 4.4: • Indication for treatment of patients with β-hemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of CASGEVY must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Collection of unmodified rescue $CD34^+$ stem cells is required prior to myeloablative conditioning and infusion with CASGEVY, as outlined in SmPC Section 4.2. • Guidance for administering unmodified rescue cells in the event of neutrophil engraftment failure is provided in SmPC Sections 4.2 and 4.4. • Recommendations for monitoring neutrophil counts and managing infections are provided in SmPC Section 4.4. PL Sections 2 and 4: • Information on what to expect if engraftment fails is provided in PL Section 2. • Advice on how to identify symptoms of infection and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine <u>Additional Risk Minimisation Measures</u> • Guide for HCPs • Patient Card • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD ages 12 to 35 years • Study 151 in subjects with SCD ages 2 to 11 years • Study 161 in subjects with TDT or SCD ages 12 to 35 years

	• Study 171 in subjects with SCD ages 12 to 35 years See Section II.C of this summary for an overview of the post-authorisation development plan.
Gene editing-related oncogenesis (Important potential risk)	
Evidence for linking the risk to the medicine	Gene editing-related oncogenesis is considered an important risk as it is theoretically possible after Casgevy infusion. In the clinical programme, there have been no reports of blood cancers due to treatment with Casgevy and no potential identified in nonclinical and in silico studies; therefore, this risk is considered potential.
Risk factors and risk groups	There have been no reports of gene editing-related oncogenesis in follow-up of up to 4 years after Casgevy infusion; therefore, no risk factors or risk groups were identified in the clinical programme.
Risk minimisation measures	<u>Routine Risk Minimisation Measures</u> SmPC Section 4.4 • Description that there have been no cases of myelodysplasia, leukaemia, or lymphoma from the clinical studies • As a theoretical risk, recommend monitoring at least annually (including complete blood count) for 15 years after treatment. Restricted prescription medicine <u>Additional Risk Minimisation Measures</u> • Guide for HCPs • Patient Card • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 131 Long term follow-up study in subjects with TDT and SCD See Section II.C of this summary for an overview of the post-authorisation development plan.
Long-term effects (Missing information)	
Risk minimisation measures	<u>Routine Risk Minimisation Measures</u> SmPC Section 4.4: • Recommendation for long-term follow up is provided in SmPC Section 4.4. PL Section 2: • Expectations for long-term monitoring are described in PL Section 2. Restricted prescription medicine <u>Additional Risk Minimisation Measures</u> • Guide for HCPs • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 101[a] (PASS) • HCP Survey (PASS) *Efficacy studies that will provide relevant safety results:* • Study 131 Long term follow-up study in subjects with TDT and SCD See Section II.C of this summary for an overview of the post-authorisation development plan.

Pregnancy and lactation (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.6: • Recommendations for contraception use, breastfeeding, and pregnancy, including a negative pregnancy test prior to the start of any treatment, are provided in SmPC Section 4.6. • CASGEVY must not be administered during pregnancy or breastfeeding due to risks associated with myeloablative conditioning, as stated in SmPC Section 4.6. PL Section 2: • Expectations for use of contraception, pregnancy testing, and breastfeeding are described in PL Section 2. • Advice for talking to the doctor prior to starting treatment is given in PL Section 2. Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 101[a] (PASS; pregnancy outcomes) *Efficacy studies that will provide relevant safety results:* • Study 131 Long term follow-up study in subjects with TDT and SCD See Section II.C of this summary for an overview of the post-authorisation development plan.
Use in patients >35 years of age (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.2 • Recommendation to consider the benefits of treatment against the risks of HSCT is provided in SmPC Section 4.2. Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.

AE: adverse event; HSCT: haematopoietic stem cell transplant; PASS: post-authorisation safety study; PL: Package Leaflet; SCD: sickle cell disease; SmPC: Summary of Product Characteristics; TDT: transfusion-dependent β-thalassemia

[a] Study 101 (PASS) Progress Reports 1, 2, and 3 and Interim Report 1 will be provided as a special obligation in the context of a conditional MA.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Study 101: Post-authorisation safety study *(PASS)*

Purpose of the study: To evaluate the long-term safety and effectiveness outcomes in patients who received CASGEVY for treatment of TDT or SCD in comparison to patients receiving allogenic HSCT

Study 111: Study in subjects with TDT ages 12 to 35 years

Purpose of the study: To evaluate the safety and efficacy of CASGEVY in subjects with TDT

Study 121: Study in subjects with SCD ages 12 to 35 years

Purpose of the study: To evaluate the safety and efficacy of CASGEVY in subjects with SCD

Study 131: Long-term follow-up study in subjects with TDT and SCD
Purpose of the study: To evaluate the long-term safety and efficacy for 15 years in patients who received CASGEVY for treatment of TDT or SCD

Study 151: Study in subjects with SCD ages 2 to 11 years
Purpose of study: To evaluate the safety and efficacy of CASGEVY in paediatric subjects with SCD

Study 161: Study in subjects with TDT or SCD ages 12 to 35 years
Purpose of study: To evaluate the foetal hemoglobin levels over time, safety, and efficacy of CASGEVY in subjects with TDT or SCD

Study 171: Study in subjects with SCD ages 12 to 35 years
Purpose of study: To evaluate the safety and efficacy of CASGEVY in subjects with SCD, βS/βC genotype

II.C.2 Other studies in post-authorisation development plan

Healthcare Professional (HCP) Survey to assess the effectiveness of the additional risk minimisation measures (aRMMs) for exagamglogene autotemcel (Casgevy) *(PASS)*
Purpose of the study: To assess the HCPs' understanding of the important safety information detailed in the Guide for HCPs, the HCPs' awareness of the aRMM tools, and the HCPs' utilisation of aRMM tools (behaviour)

PART VII Annexes to the Risk Management Plan

Annex 4 Specific adverse event follow-up form

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Annex 4 Specific adverse event follow-up form

Pregnancy and Lactation Questionnaire

- **Please complete form and appendices (as applicable) in accordance with local laws and regulations (e.g., personal data protection).**
- Completed forms are sent to Vertex Patient Safety via Email: [redacted] or Fax: [redacted]

Date of Report *(dd/mmm/yyyy)*:			☐ Initial Report ☐ Follow-up	
Patient *(recipient of drug)* **Name/Initials/ID:** **DOB:** ☐Female ☐Male partner		**Maternal:** Age	Height ☐ cm / ☐ in	Weight ☐ kg / ☐ lb
Vertex Drug(s)	**Start Date**	**End Date**		**Dose, Frequency, Route**
		☐ Ongoing		
Pregnancy Outcome ☐Ongoing ☐Live Delivery ☐Spontaneous Abortion ☐Therapeutic Abortion ☐Elective Termination ☐Stillbirth ☐Unknown				
Infant Information ☐Female ☐Male	**APGAR** 1 min: 5 min:	Height ☐ cm / ☐ in	Weight ☐ kg / ☐ lb	Weight-for-gestation age percentile
NARRATIVE *(Pregnancy details, use of IVF, gestational week, LMP, estimated date of conception, estimated due date; Birth outcome: normal / abnormal).*				
RELEVANT MATERNAL AND PATERNAL HISTORY / RISK FACTORS *(e.g., comorbidities, genetic disorders, reproductive complications, alcohol or drug use)*				
Maternal: Paternal:				
RELEVANT MATERNAL CONCOMITANT MEDICATIONS	**INDICATION**	**START DATE**	**END DATE**	**DOSE, FREQUENCY, ROUTE**
MATERNAL FETAL HEMOGLOBIN, HEMOGLOBIN A, AND TOTAL HEMOGLOBIN LEVELS *(Please provide values during pregnancy, including collection date, local reference range, and unit).*				
Report Completed By (Name/Title):				
Institution / Country Email	Fax Phone		SIGNATURE / DATE	
If unable to provide information requested above, please provide <u>additional</u> contact information (e.g., OBGYN, Pediatrician):				
Has consumer <u>denied</u> permission for his/her physician or designee to be contacted? ☐ Yes ☐ No				

Appendix 1 Information for Adverse Events Associated with Pregnancy or Breastfeeding

Adverse Event (if associated with pregnancy or breastfeeding*):			**Start Date**	**Outcome Date**
Seriousness Criteria *(if applicable)* ☐ Hospitalization (requires or prolongs admission) Admission:_____Discharge:_____ ☐ Important Medical Event per medical judgement (may jeopardize patient or require intervention to prevent 1 of the other serious outcomes) ☐ Life-threatening (at risk of death at time of event) ☐ Permanent Disability ☐ Congenital Anomaly ☐ Death Date of Death:_____			**Event Outcome** ☐ Recovered / Resolved ☐ Recovering / Resolving ☐ Recovered / Resolved w/ Sequelae ☐ Not Recovered / Not Resolved (Ongoing) ☐ Fatal ☐ Unknown	
Vertex Drug Casgevy (exa-cel)	**Related**† ☐	**Not Related**‡ ☐	**Suspected etiology(ies):**	
Treatment(s)	**Start Date**	**End Date**	**Dose, Route, Frequency**	**Response to Treatment**
Did the event require transfusions?	**Dates**	**Units**	**Response**	
☐ **pRBC**				
☐ **Platelets**				
Narrative *(please include diagnostic test results, total hemoglobin, fetal hemoglobin, hemoglobin A, platelet counts, and absolute neutrophil counts before, during, after events and most recently, as well as all other pertinent information)*				

**For all other reportable adverse events, please report to Vertex Global Patient Safety using the standard reporting form in accordance with standard procedures.*

†*"Related" means there is an association between the event and the administration of the Vertex product and at least a plausible mechanism for the event to be related to the Vertex product.*

‡*"Not Related" means the event is unlikely to be related to the Vertex product and likely to be related to factors or an etiology other than the Vertex product.*

Appendix 2 Infant Follow-up Information

INFANT FOLLOW-UP ☐ 6-MONTHS ☐ 12-MONTHS

Date of Birth *(dd/mmm/yyyy)*:	Status: ☐ Normal ☐ Abnormal	Height ☐ cm / ☐ in	Weight ☐ kg ☐ lb	Weight-for-gestation age percentile

Adverse Event (if associated with pregnancy*):	**Start Date**	**Outcome Date**

Seriousness Criteria *(if applicable)*

☐ Hospitalization (requires or prolongs admission)
Admission:_____Discharge:_____
☐ Important Medical Event per medical judgement (may jeopardize patient or require intervention to prevent 1 of the other serious outcomes)
☐ Life-threatening (at risk of death at time of event)
☐ Permanent Disability
☐ Congenital Anomaly
☐ Death Date of Death:_____

Event Outcome

☐ Recovered / Resolved
☐ Recovering / Resolving
☐ Recovered / Resolved w/ Sequelae
☐ Not Recovered / Not Resolved (Ongoing)
☐ Fatal
☐ Unknown

Vertex Drug	**Related†**	**Not Related‡**	**Suspected etiology(ies):**
Casgevy (exa-cel)	☐	☐	

Treatment(s)	**Start Date**	**End Date**	**Dose, Route, Frequency**	**Response to Treatment**

Narrative

*For all other reportable adverse events, please report to Vertex Global Patient Safety using the standard reporting form in accordance with standard procedures.

† *"Related" means there is an association between the event and the administration of the Vertex product and at least a plausible mechanism for the event to be related to the Vertex product.*

‡ *"Not Related" means the event is unlikely to be related to the Vertex product and likely to be related to factors or an etiology other than the Vertex product.*

Platelet Engraftment Questionnaire

Please complete the form and appendices (as applicable) in accordance with local laws and regulations (e.g., personal data protection)
Completed forms are sent to Vertex Patient Safety via Email: G[redacted]. or Fax: [redacted]

Initials or Subject ID	Date of Birth:	☐ Female ☐ Male	Height cm / in	Weight kg / lb
Indication:	Date of exa-cel infusion:	Exa-cel Dose ($\times 10^6$/kg):	Lot #/Exp Date	
Date of neutrophil engraftment:		Date of platelet engraftment:		
Conditioning Agent(s):		Conditioning dose, freq, dates:		

1. **Were there any clinical signs/symptoms attributed to the time to platelet engraftment, including any bleeding complications or findings suggestive of sepsis, VOD, DIC, or microangiopathy, etc.?** ☐ Yes ☐ No

   If yes, please provide details for the adverse event(s) in the appendix of this form, including site of bleeding if applicable.

2. **Please provide your overall assessment of the reason(s) for the prolonged time to platelet engraftment.**

3. **Was the subject refractory to platelet transfusions?** ☐ Yes ☐ No

   If yes, please provide pre- and post-transfusion platelet counts supporting this (including dates of refractoriness).

4. **Was a bone marrow analysis performed?** ☐ Yes ☐ No

   If yes, please provide sampling date(s), sample type (aspirate, biopsy, etc.), final reports, and overall interpretation of results.

5. **Were any cytogenetic or gene sequencing tests performed (e.g., karyotype, FISH, next generation sequencing for somatic or germline mutations)?** ☐ Yes ☐ No

   If yes, please provide sampling date(s), sample type (bone marrow aspirate, peripheral blood), final reports, and overall interpretation of results.

6. **Was any relevant testing performed (e.g., HLA- or platelet-specific antibodies, DIC panel, infectious disease work-up)?** ☐ Yes ☐ No

   If yes, please provide date(s), assessment, final reports, and overall interpretation of results.

7. **Were there any therapeutic interventions for the thrombocytopenia (e.g., steroids, IVIG, TPO mimetics)?** ☐ Yes ☐ No

Medication Name	**Start** (dd-mmm-yyyy)	**End** (dd-mmm-yyyy)	**Dose, Route, Freq.**	**Indication**	**Response**

8. **Please provide any relevant history and risk factors (e.g., comorbidities, autoimmune disorders, liver disease, genetic disorders).**

9. **Does the patient have an intact spleen (i.e., not surgically splenectomized)?** ☐ Yes ☐ No

   If yes, was splenomegaly present? Please include dates, measurements, and method of assessment (e.g., imaging, palpation).

10. **Has the subject taken medications that could interfere with platelet production or survival (e.g., sulfonamides, quinidines, heparin, ADP receptor antagonists, glycoprotein IIb/IIIa inhibitors, supplements)?** ☐ Yes ☐ No

Medication Name	**Start** (dd-mmm-yyyy)	**End** (dd-mmm-yyyy)	**Dose, Route, Freq.**	**Indication**	**Response**

11. **Please provide relevant laboratory counts, including baseline counts (e.g., before conditioning, before exa-cel):**

Date (dd-mmm-yyyy)	Platelet count (units)	Neutrophil count (units)	Hemoglobin (units)

Report Completed by (Name / Title):

Institution / Country

Fax

Email

Phone

Investigator or Treating Physician Name:

Reporter or Investigator Signature / Date:

Appendix: Information for Adverse Events Associated With Time to Platelet Engraftment

<table>
<tr><td colspan="3">Adverse Event (if associated with time to platelet engraftment*):</td><td colspan="2">Start Date</td><td>End Date</td></tr>
<tr><td colspan="3">Seriousness Criteria (if applicable)
☐ Hospitalization Admission: Discharge:
☐ Important Medical Event
☐ Life-threatening
☐ Permanent Disability
☐ Congenital Anomaly
☐ Death Date of Death:</td><td colspan="3">Event Outcome
☐ Recovered / Resolved
☐ Recovering / Resolving Date:
☐ Recovered / Resolved w Sequelae Date:
☐ Not Recovered / Not Resolved (Ongoing)
☐ Fatal
☐ Unknown</td></tr>
<tr><td>Vertex Drug(s)</td><td>Related</td><td>Not Related</td><td colspan="3" rowspan="2">Suspected etiology(ies):</td></tr>
<tr><td>Exa-cel</td><td>☐</td><td>☐</td></tr>
<tr><td>Treatment(s)</td><td>Start Date</td><td>End Date</td><td>Dose, Route, Frequency</td><td colspan="2">Response to Treatment</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td>Did the event require transfusions?</td><td>Dates</td><td>Units</td><td colspan="3">Response</td></tr>
<tr><td>☐ pRBC</td><td></td><td></td><td colspan="3"></td></tr>
<tr><td>☐ Platelets</td><td></td><td></td><td colspan="3"></td></tr>
<tr><td colspan="6">Narrative (please include diagnostic test results, platelet counts before, during, after events and most recently, as well as all other pertinent information)</td></tr>
</table>

**Please report all other Safety Information to Vertex Global Patient Safety in accordance with standard procedures.*

Neutrophil Engraftment Failure Questionnaire

Please complete the form and appendices (as applicable) in accordance with local laws and regulations (e.g., personal data protection).
Completed forms are sent to Vertex Patient Safety via Email: [redacted] or Fax: [redacted].

Initials or Subject ID	Date of Birth:	☐ Female ☐ Male	Height cm / in	Weight kg / lb
Indication:	Date of exa-cel infusion:	Exa-cel Dose ($\times 10^6$/kg):	Lot #/Exp Date	
Date of neutrophil engraftment:		Date of platelet engraftment:		
Conditioning Agent(s):		Conditioning dose, freq, dates:		

1. **Were there any clinical signs/symptoms attributed to the neutrophil engraftment failure, including any infections, reactivations, persistent fever, findings suggestive of sepsis, etc.?** ☐ Yes ☐ No

   If yes, please provide details for the adverse event(s) in the appendix of this form, including pathogen if applicable.

2. **Please confirm and describe the criteria met for neutrophil engraftment failure:**

   a. Primary graft failure (no evidence of engraftment or hematological recovery) ☐ Yes ☐ No

   b. Secondary graft failure (loss of previously functioning graft) ☐ Yes ☐ No

3. **Please provide your overall assessment of the reason(s) for the neutrophil engraftment failure.**
4. **Was a second transplant required?** ☐ Yes (autologous backup/unedited cells) ☐ Yes (allogeneic transplant) ☐ Other ☐ None

   a. Please provide a description of the therapy, timing/dates, clinical response, etc.

5. **Was a bone marrow analysis performed?** ☐ Yes ☐ No

   If yes, please provide sampling date(s), sample type (aspirate, biopsy, etc.), final reports, and overall interpretation of results.

6. **Were any cytogenetic or gene sequencing tests performed (e.g., karyotype, FISH, next generation sequencing for somatic or germline mutations)?** ☐ Yes ☐ No

   If yes, please provide sampling date(s), sample type (bone marrow aspirate, peripheral blood), final reports, and overall interpretation of results.

7. **Was any relevant testing performed (e.g., infectious disease work-up)?** ☐ Yes ☐ No

   If yes, please provide date(s), assessment, final reports, and overall interpretation of results.

8. **Were there any therapeutic interventions for the prolonged neutropenia (e.g., G-CSF, EPO, TPO)?** ☐ Yes ☐ No

Medication Name	**Start** (dd-mmm-yyyy)	**End** (dd-mmm-yyyy)	**Dose, Route, Freq.**	**Indication**	**Response**

9. **Please provide any relevant history (e.g., comorbidities, genetic disorders, infections).**
10. **Does the patient have an intact spleen (i.e., not surgically splenectomized)?** ☐ Yes ☐ No

    If yes, was splenomegaly present? Please include dates, measurements, and method of assessment (e.g., imaging, palpation).

11. **Please provide any risk factors present:**
    - **a. Red blood cell transfusions:**
        - i. Average number of transfusions and units per year before exa-cel
        - ii. Number of transfusions and units after exa-cel
    - **b. History of iron overload? ☐ Yes ☐ No**
        - i. Liver iron content before exa-cel (date)
        - ii. Liver iron content after exa-cel (date)
        - iii. Cardiac iron content before exa-cel (date)
        - iv. Cardiac iron content after exa-cel (date)
    - **c. Viral infection (e.g., CMV, EBV, HHV, HCV)? ☐ Yes ☐ No**
        - i. Date of initial diagnosis, prior treatments, status before exa-cel.
        - ii. Was there a reactivation after exa-cel? If yes, please provide dates, viral load, treatments, etc.
    - **d. Please provide all additional risks factors:**

12. **Has the subject taken medications that could interfere with neutrophil production or survival (e.g., antimicrobials, quinidines, ganciclovir, immunosuppressants)?** ☐ Yes ☐ No

Medication Name	**Start** (dd-mmm-yyyy)	**End** (dd-mmm-yyyy)	**Dose, Route, Freq.**	**Indication**	**Response**

13. **Please provide relevant laboratory counts, including baseline counts (e.g., before conditioning, before exa-cel):**

Date (dd-mmm-yyyy)	**Neutrophil Count**	**Neutrophil %**	**WBC count**	**Hgb**	**Platelets**	**Lymphocyte Count**	**Lymphocyte %**	**CD4+, CD8+, CD19+, NK cells**

Report Completed by (Name / Title):	**Investigator or Treating Physician Name:**
Institution / Country Fax	**Reporter or Investigator Signature / Date:**
Email Phone	

Appendix: Information for Adverse Events Associated With Neutrophil Engraftment Failure

<table>
<tr><td colspan="3">Adverse Event (if associated with time to neutrophil engraftment*):</td><td colspan="2">Start Date</td><td>End Date</td></tr>
<tr><td colspan="3">Seriousness Criteria (if applicable)
☐ Hospitalization Admission: Discharge:
☐ Important Medical Event
☐ Life-threatening
☐ Permanent Disability
☐ Congenital Anomaly
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<tr><td>Exa-cel</td><td>☐</td><td>☐</td></tr>
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</table>

**Please report all other Safety Information to Vertex Global Patient Safety in accordance with standard procedures.*

Haematologic Malignancy Questionnaire

Please complete the form and appendices (as applicable) in accordance with local laws and regulations (e.g., personal data protection).

Completed forms are sent to Vertex Patient Safety via Email: [redacted] or Fax: [redacted].

Initials or Subject ID	Date of Birth:	☐ Female ☐ Male	Height cm / in	Weight kg / lb
Indication:	Date of exa-cel infusion:	Exa-cel Dose ($\times 10^6$/kg):	Lot #/Exp Date	
Date of neutrophil engraftment:		Date of platelet engraftment:		

1. **Please provide details of the haematologic malignancy using the appendix of this form, including specific treatments/procedures for the event, such as chemotherapy/radiotherapy or transplant.**
2. **Were any cytogenetic or gene sequencing tests performed (e.g., karyotype, FISH, next generation sequencing for somatic or germline mutations)? ☐ Yes ☐ No**

   If yes, please provide the type of testing, sampling date(s), sample type (bone marrow aspirate, peripheral blood), final reports, and overall interpretation of results.
3. **Was a bone marrow histopathology and/or flow cytometry performed? ☐ Yes ☐ No**

   If yes, please provide sampling date(s), sample type (aspirate, biopsy, etc.), final reports, and overall interpretation of results.
4. **Is there prior history of other malignancies or genetic syndromes, including myelodysplasia syndrome (MDS)? ☐ Yes ☐ No**

   If yes, please provide details.
5. **Is there family history of other malignancies or genetic syndromes? ☐ Yes ☐ No**

   If yes, please provide details.
6. **Please provide any other relevant history (e.g., comorbidities, genetic disorders, infections).**
7. **Please provide the most recent EBV and CMV titers with dates**
8. **Please provide any risk factors present:**

   a. **History of smoking? ☐ Yes ☐ No**
   If yes, please provide the average amount of smoking (e.g., 1 pack per day).

   b. **Was busulfan used as the myeloablative agent? ☐ Yes ☐ No**
   If yes, please provide dosing frequency and AUC (area under the concentration versus time curve, if available.

   c. **Prior/Current myeloablative agent (if not busulfan), chemotherapy, radiochemistry, or immunosuppression? ☐ Yes ☐ No**

Medication	**Start** (dd-mmm-yyyy)	**End** (dd-mmm-yyyy)	**Dose, Route, Freq.**	**Indication**

d. Prior/Current chemical exposure (e.g., benzene, insecticides)? ☐ Yes ☐ No

Chemical Name	**Start** (dd-mmm-yyyy)	**End** (dd-mmm-yyyy)	**Dose, Route, Freq.**	**Indication**

14. **Please provide relevant hematology laboratory counts, including baseline (e.g., before conditioning, before exa-cel):**

Date (dd-mmm-yyyy)	**WBC count**	**Hgb**	**Platelets**	**Peripheral blood smear findings (e.g., blasts)**

Report Completed by (Name / Title):		**Investigator or Treating Physician Name:**
Institution / Country	Fax	**Reporter or Investigator Signature / Date:**
Email	Phone	

Appendix: Information for Haematologic Malignancy Adverse Events

<table>
<tr><td colspan="3">Adverse Event:</td><td colspan="2">Start Date</td><td>End Date</td></tr>
<tr><td colspan="3">Seriousness Criteria (if applicable)
☐ Hospitalization Admission: Discharge:
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<tr><td></td><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="6">Narrative(please include diagnostic test results, any results from cytogenic or gene sequencing tests, risk factors [chemotherapy, radiotherapy, immunosuppression, chemical exposures], prior/current history of malignancies, family history of malignancy, peripheral blood smear findings [e.g., blasts], as well as all other pertinent information)</td></tr>
</table>

**Please report all other Safety Information to Vertex Global Patient Safety in accordance with standard procedures.*

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Prior to the use of Casgevy (exagamglogene autotemcel) in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme with the National Competent Authorities.

The MAH shall ensure that in each Member State where Casgevy is marketed, all healthcare professionals (HCPs) and patients/carers who are expected to prescribe, use, or oversee the administration of Casgevy have access to/are provided with the following 2 educational packages aimed at highlighting the important identified and potential risks of Casgevy. These packages will be translated in the local language to ensure understanding of proposed mitigation measures by physicians and patients:

- **The Physician Educational Material consists of**
  - Guide for Healthcare Professionals;
  - Summary of Product Characteristics;
  - Guide for Patients/Carers;
  - Patient Card.
- **The Patient Information Pack consists of**
  - Guide for Patients/Carers;
  - Patient Card;
  - Patient Information Leaflet

Guide for Healthcare Professionals

- The HCP should inform patients treated with Casgevy that there is an important identified risk of delayed platelet engraftment and important potential risks of neutrophil engraftment failure and gene editing-related oncogenesis; and details on how these risks can be minimised.

When presenting Casgevy as a treatment option and before a treatment decision is made, the HCP should discuss the risk-benefit of Casgevy, including the following:

- Delayed platelet engraftment
  - Platelet counts should be monitored and managed according to standard guidelines and medical judgement. Blood cell count determination and other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise.
  - Patients should be counselled regarding the risk of delayed platelet engraftment, what symptoms and signs to be aware which could indicate bleeding, and the need to seek medical assistance if they experience any signs or symptoms suggestive of bleeding.
- Neutrophil engraftment failure
  - Patients should be monitored for absolute neutrophil counts and infections and should be managed according to standard guidelines and medical judgement. In the event of neutrophil engraftment failure, patients should be infused with unmodified rescue $CD34^+$ stem cells.
  - Patients should be counselled regarding the fact that if they were to experience neutrophil engraftment failure after treatment with Casgevy, they would require an

infusion of back-up $CD34^+$ stem cells and would not obtain the benefit of Casgevy treatment and still be exposed to possible long-term risks.

- Gene editing-related oncogenesis
  - Gene editing-related oncogenesis is a theoretical risk. After treatment with Casgevy, patients should be monitored annually (including complete blood count) according to standard guidelines and medical judgement. If blood and bone marrow samples are taken for the diagnosis of haematologic malignancy, HCPs should take additional samples for analysis by the MAH to evaluate the association of malignancy with Casgevy treatment, should a malignancy be confirmed.
  - Patient should be counselled regarding the theoretical risk of gene editing-related oncogenesis and to seek medical attention if signs or symptoms of myelodysplasia, leukaemia, and lymphoma.
- The HCP should provide the Patient Card and Guide for Patients/Carers to patients/carers.
- There is limited information regarding long-term effects. Therefore, participation in the long-term, registry-based study evaluating the long-term safety and effectiveness outcomes in patients who received Casgevy for treatment of TDT or SCD is encouraged. The HCP should remind patients about the importance to enroll in the 15-year, registry-based study of the long-term effects and how to obtain further information.

Patient Card

- This card is to inform HCPs that the patient has received Casgevy infusion.
- The patient should show the Patient Card to a doctor or nurse whenever they have medical appointments.
- The patient should have blood tests as directed by the doctor.
- The patient should seek medical advice for any signs of low platelet cell or white blood cell levels: severe headache, abnormal bruising, prolonged bleeding, or bleeding without injury (such as nosebleeds, bleeding from gums, blood in the urine, stool, or vomit, or coughing up blood), fever, chills, or infections.
- Blood cancers are a theoretical risk. The patient should seek medical advice for any signs of fatigue, unexplained fever, night sweats, unexplained weight loss, frequent infections, shortness of breath, or swelling of lymph glands.

Guide for Patients/Carers

The guide explains the importance to fully understand the risk-benefit of Casgevy treatment and that there is limited information about the long-term effects.

Therefore, before a decision is made about starting the therapy, the doctor will discuss the following with the patient/carer:

- How the important identified risk of delayed platelet engraftment and important potential risk of neutrophil engraftment failure can be recognised and minimised, including the need for monitoring of platelet and neutrophils regularly with regular blood tests until they have returned to a safe level.

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